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## **BRUCELLOSIS**

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### **Epidemiology**

*Brucella* species are small, nonmotile, gram-negative coccobacilli. The species that infect humans are *Brucella abortus*, *B. melitensis*, *B. suis* and, rarely, *B. canis*.

Four *Brucella* spp. can cause infection in humans:

- *Brucella melitensis*, which is found in goats, sheep and camels, is the most widespread and is the most virulent
- *Brucella abortus*, which is found in cattle and camels, is less virulent
- *Brucella suis*, which is found in pigs, is also less virulent
- *Brucella canis*, which is found in dogs, is the least common.

Other animals, including wildlife, may provide a reservoir for brucellae.

Brucellosis is a zoonotic disease of wild and domestic animals. Humans are accidental hosts. Brucellosis is transmitted to humans by contact with tissues, blood, urine, vaginal discharges, aborted fetuses and especially the placentas of infected animals; also by ingestion of unpasteurized milk or milk products from infected animals.

The disease is predominantly an occupational illness in persons such as farm and livestock workers, veterinarians, slaughterhouse employees, meat inspectors and lab personnel. Isolated cases of infection with *Brucella canis* also occur in animal handlers from contact with dogs, especially beagles.

*B. canis* is the species of *Brucella* species that can infect dogs. This species has occasionally been transmitted to humans, but the vast majority of dog infections do not result in human illness. Although veterinarians exposed to blood of infected animals are at risk, pet owners are not considered to be at risk for infection. This is partly because it is unlikely that they will come in contact with blood, semen, or placenta of the dog. The bacteria may be cleared from the animal within a few days of treatment; however re-infection is common and some animal body fluids may be infectious for weeks. Immunocompromised persons (cancer patients, HIV-infected individuals, or transplantation patients) should not handle dogs known to be infected with *B. canis*.

Infection is transmitted by inoculation through cuts and abrasions in the skin, by inhalation of contaminated aerosols, by contact with the conjunctival mucosa, or by oral ingestion.

There is no danger from eating cooked meat products because the disease-causing bacteria are not normally found in muscle tissue and they are killed by normal cooking temperatures. The disease may be transmitted to humans when slaughtering infected animals or when processing contaminated organs from freshly killed animals.

Human to human transmission has been rarely documented.

*Brucella* spp. have a high probability for use in biologic terrorism and are highly infectious via the aerosol route. It is estimated that inhalation of only ten to 100 bacteria is sufficient to cause disease in man. The relatively long and variable incubation period (5-60 days), and the fact that many infections are asymptomatic under natural conditions has made it a less desirable agent for weaponization, although large aerosol dosage may shorten the incubation period and increase the clinical attack rate.

Most cases result from travel outside the United States or from ingestion of unpasteurized milk products.

The incubation period varies from less than one week to several months, but most patients become ill within three to four weeks of exposure.

### **Clinical Description**

Brucellosis is a systemic infection that can involve any organ or organ system. Onset of illness can be acute or insidious. Manifestations are nonspecific and include fever, night sweats, weakness, malaise, anorexia, weight loss, arthralgia, myalgia, abdominal pain and headache. The clinical picture in human brucellosis can be misleading and cases in which gastrointestinal, respiratory, dermal, or neurologic manifestations predominate are not uncommon.

Physical findings include lymphadenopathy, hepatosplenomegaly and, occasionally, arthritis. Serious complications include meningitis, endocarditis and osteomyelitis.

Common complications are cardiovascular infections, endocarditis, cutaneous, gastrointestinal, genitourinary, orchitis, neurologic, osteoarticular, sacroiliitis, spondylitis and pulmonary.

### **Laboratory Tests**

Beware of false positives: The Centers for Disease Control and Prevention (CDC) recommends that *Brucella* serology testing only be performed using tests cleared or approved by the Food and Drug Administration (FDA) or validated under the Clinical Laboratory Improvement Amendments (CLIA) and shown to reliably detect the presence of *Brucella* infection. Results from these tests should be considered supportive evidence for recent infection only and interpreted in the context of a clinically compatible illness and exposure history. EIA is not considered a confirmatory *Brucella* antibody test; positive screening test results should be confirmed by *Brucella*-specific agglutination (i.e., BMAT or standard tube agglutination test) methods.

Cross-reactions and false-positive test results can occur in *Brucella* antibody tests. The primary immunodeterminant and virulence factor for *Brucella* species is the cell wall surface lipopolysaccharide, which is antigenically similar to the lipopolysaccharide of other gram-negative rods. False-positive *Brucella* antibody test results can be caused by cross-reactivity of antibodies to *Escherichia coli* O157, *Francisella tularensis*, *Moraxella phenylpyruvica*, *Yersinia enterocolitica* and certain *Salmonella* species. Most cross-reacting antibodies are IgM, making interpretation of any IgM assay difficult because of false positivity. Therefore, results obtained using EIA should be confirmed by a reference method.

Testing of persons with compatible signs and symptoms for brucellosis should be supported by a thorough history that reveals likely exposure through travel to an area where brucellosis is endemic, consumption of an unpasteurized dairy product, hunting potentially infected wildlife species, or laboratory exposure. Testing of persons in the absence of a suggestive exposure increases the likelihood of false-positive results and lowers the overall positive predictive value of the assay used. Rapid *Brucella* antibody assays can be useful as screening tools when results are interpreted in the context of performance characteristics of the particular test; however, the CDC recommends that all positive results obtained by rapid serologic assays be confirmed with *Brucella*-specific agglutination testing. For questions about risk factors or to request

confirmatory testing for brucellosis in patients with strong evidence of exposure, health-care providers should contact their local or state health department.

- Culture from blood, bone marrow or other tissues, or from discharges of the patient are still the standard methods and are often effective during the acute phase. A variety of media will support the growth of *Brucella* species. Laboratory personnel should be alerted to incubate cultures for a minimum of four weeks and to use proper precautions for protection against laboratory-acquired infection. Lysis-centrifugation techniques may shorten the time necessary to isolate *Brucella* organisms. Reliance should not be placed on gallery type rapid identification systems as these have misidentified *Brucella* as *Moraxella phenylpyruvica*, with serious consequences for laboratory staff.
- A polymerase chain reaction test is available in OPH for environmental samples and confirmation of subcultures.
- IFAC: immunofluorescent antibody test on a pure isolate
- A fourfold or greater rise in *Brucella* agglutination titer between acute and convalescent serum specimens obtained two (2) or more weeks apart. Serologic diagnosis is discouraged because too often an initial serum is sent without follow up serum.
- *Brucella* agglutination titer of 1:160 or greater in one or more serum specimens obtained after the onset of clinical symptoms that are consistent with those listed on the previous page under case definition.

The serum agglutination test (SAT), which is the most commonly used test, will detect antibodies against *B.abortus*, *B.suis* and *B.melitensis*, but not *B.canis*. Detection of antibodies against *B. canis* requires use of *B.canis*-specific antigen. Although a single titer is not diagnostic, most patients with active infection have titers of 1:160 or greater. Lower titers may be found early in the course of infection. Elevated concentrations of immunoglobulin (Ig) G agglutinins are found in acute infection, chronic infection and relapse. When interpreting SAT titers, the possibility of cross-reactions of *Brucella* antibodies with those against other gram-negative bacteria, such as *Vibrio cholerae*, *Yersinia enterocolitica* serotype 09, *Francisella tularensis* and *Vibrio cholerae*, should be considered. False-negative reactions due to blocking antibodies are seen and dilutions of 1:640 should be made to avoid the prozone phenomenon. A titer greater than 1:160 is normally considered positive, as is a four-fold or greater rise in titer. Enzyme immunoassay (EIA) is a sensitive method for determining IgG, IgA and IgM anti-*Brucella* antibodies, but until better standardization is established, EIA should be used for suspected cases with negative SAT titers or for evaluation of patients with suspected relapse or reinfection.

When sending serum samples in to the Central Laboratory in New Orleans, collect one red-topped tube of blood for each specimen. The blood should either be spun down and the sera sent or the whole blood sent refrigerated. It is usually better to hold the acute sera until the convalescent sera has been collected and forward both at the same time. If holding acute sera until collection of convalescent specimen, the acute sera must be spun down and sera saved.

- A clinical specimen containing fluorescent-antibody positive bacteria.

## Surveillance

Brucellosis is a condition reportable within twenty-four hours by phone.

## Case Definition

**Clinical description:** An illness characterized by acute or insidious onset of fever, night sweats, undue fatigue, anorexia, weight loss, headache and arthralgia.

### Laboratory criteria for diagnosis

- Isolation of *Brucella* spp. from a clinical specimen, or
- Fourfold or greater rise in *Brucella* agglutination titer between acute- and convalescent-phase serum specimens obtained greater than or equal to two weeks apart and studied at the same laboratory, or
- Demonstration by immunofluorescence of *Brucella* spp. in a clinical specimen.

### Case classification

Probable: a clinically compatible case that is epidemiologically linked to a confirmed case or that has supportive serology (i.e., *Brucella* agglutination titer of greater than or equal to 160 in one or more serum specimens obtained after onset of symptoms)

Confirmed: a clinically compatible illness that is laboratory confirmed.

### **Intervention**

The purpose of intervention is to identify cases, to trace source(s) of infection, to identify possible contacts of infection and to assist the U.S. Department of Agriculture (by source identification) with the eradication of brucellosis in cattle, swine and other animals.

- Upon receipt of a report of brucellosis, contact the physician and/or hospital to confirm the diagnosis.
- Identify the patient's occupation and/or source of infection.
- Interview the patient and fill out the Brucellosis Case Investigation form. This will help determine the source of infection: foreign travel, occupation, or laboratory acquisition.

Prophylaxis using killed and live attenuated human vaccines have been available in many countries but are of unproven efficacy.

For prophylaxis against brucellosis, the same antibiotic therapy as that used for treatment is recommended (see below) for six weeks. Prophylaxis is recommended for workers exposed to the bacteria. A significant exposure has to be determined.

### **Case Management - Treatment**

- To decrease the incidence of relapse, many experts recommend combination therapy. By order of effectiveness (highly effective first)
  - Triple therapy doxycycline + rifampin + aminoglycoside
  - Double therapy doxycycline + aminoglycosides
  - Double therapy doxycycline + rifampin
  - Quinolone + rifampin
  - Monotherapy (doxycycline or trimethoprim/sulfa) are associated with a high rate of relapse
  - Treatment for six weeks is more effective than the standard three weeks. Prolonged therapy is imperative for achieving a cure. Relapses generally are not caused by development of resistance but rather by premature discontinuation of antimicrobial therapy.
  - For aminoglycosides: gentamicin is as effective as streptomycin
  - The treatment recommended by the World Health Organization for acute brucellosis in adults is rifampicin 600 to 900 mg and doxycycline 200 mg daily for a minimum of six weeks.

### Doses:

- Oral doxycycline (2 to 4 mg/kg per day; maximum, 200 mg/d in 2 divided doses) or, alternatively, tetracycline (30 to 40 mg/kg per day; maximum, 2 g/d in 4 divided doses) po for four to six weeks. Cyclines should be avoided in children younger than eight years of age.

- Oral trimethoprim-sulfamethoxazole (trimethoprim, 10 mg/kg per day; maximum, 480 mg/d, and sulfamethoxazole, 50 mg/kg per day; maximum, 2.4 g/d) for four to six weeks for younger patients with a tetracycline (or trimethoprim-sulfamethoxazole if tetracyclines are contraindicated), and rifampin (15 to 20 mg/kg per day in 1 or 2 divided doses; maximum, 600 to 900 mg/d). Because of the potential emergence of rifampin resistance, rifampin monotherapy is not recommended.

**Hospital precaution and isolation:** Standard precautions and in case of draining wounds contact precautions.

### **Control Measures**

Prevention of human brucellosis depends on:

- Eradication of *Brucella* species from cattle, goats, swine and other animals.
- Pasteurization of milk and milk products for human consumption, particularly important to prevent disease in children.