**Introduction**

*Brucella* infection, also known as brucellosis, undulant fever, and Malta fever (in humans), or Bang's disease (in cattle), is an acute systemic zoonotic disease caused by *Brucella* species. The disease is characterized in humans by either a continued, intermittent, or irregular fever that can persist for days, or for up to years if it is not properly treated. Various *Brucella* species infect a variety of ruminant animals with humans infected by contact with them or animal products that contaminated by these species. The U. S. Department of Agriculture's (USDA) Animal and Plant Health Inspection Service (APHIS) has been working cooperatively with the livestock industries and state animal health authorities to eradicate brucellosis from the United States (USDA Animal and Plant Health Inspection Service Bovine Brucellosis Eradication Program). As of March 1, 2002, 48 states have achieved brucellosis-free status with no known infections. At the present time, the only known focus of *Brucella* infection left in the United States is in bison and elk in the Greater Yellowstone Area (www.aphis.usda.gov). The annual number of human cases of *Brucella* infection reported to the CDC is approximately 100 CDC (2003). The small number of cases in humans is directly associated with the control of disease in the animal population. Although brucellosis is controlled in the United States, it remains common in countries lacking standardized and effective public health and domestic animal health programs. Geographical regions currently listed as high risk are the Mediterranean Basin (Portugal, Spain, Southern France, Italy, Greece, Turkey, and North Africa), South and Central America, Eastern Europe, Asia, Africa, the Caribbean, and the Middle East Boschiroli et al (2001).

*Brucella* species are classified as overlap select agents by the U. S. Department of Health and Human Services HHS et al (2002). These agents are considered the most likely to be used in biological warfare against the United States or in other criminal acts Chang et al (2003). The ability to possess, transfer, and use this organism is strictly regulated by federal law (DHHS regulation 42 CFR Part 73 and USDA regulation 7 CFR Part 331 and 9 CFR Part 121). Clinical laboratories are required to report all positive *Brucella* species results directly to the US DHHS and must have documentation regarding the disposal or transfer of materials containing certain agents.

**Definition**

The genus *Brucella* is named after Sir David Bruce, a British military doctor who, while on the island of Malta, first recognized the organism as causing an undulant fever. Whereas the species *B.melitensis* refers to Malta, *B.abortus* refers to abortion, an outcome of infection with this species most common in cattle and other bovidae. The *B.suis* species refers to pigs, the natural host for infections by this organism, while *B.ovis* refers to sheep, *B.canis* to dogs, and *B.neotomae* to the desert wood rat, the host from which this organism was first isolated.
Classification

The taxonomy of *Brucella* species is still unresolved. On the basis of DNA-DNA hybridization studies on strains representing all species and biovars, it is proposed the genus *Brucella* contains a single species, *B. melitensis*, and that all the other recognized species should become biovars Shapiro and Wong (1999). This proposal has not been widely accepted due to the differences in animal reservoirs and the severity of clinical disease associated with different species. Currently, there are three species most associated with human disease: *B. melitensis*, which is considered the most virulent, mostly affecting sheep and goats; *B. suis*, which is considered the second most virulent and associated with disease in swine; and *B. abortus*, which is considered less virulent than the other two and is associated with disease in cattle. All of the other species of *Brucella* rarely cause disease in humans. Efforts are underway to sequence the genome of *B. melitensis* and *B. suis* DelVecchio et al (2002), Paulsen et al (2002).

Consequences

The case-fatality rate of *Brucella* infection is <2%, with most patients responding to appropriate antibiotic therapy. The main concern associated with this infection is the financial impact to agriculture practices that could occur because of an outbreak of bovine brucellosis.

Currently, there is no human vaccine available in the United States that protects against brucellosis. In animals, a live attenuated strain of *B. abortus*, called RB51, is used for immunization of cattle Schuring et al (2002). This vaccine has proven safe and effective against bovine brucellosis and exhibits negligible inference with diagnostic serology. Vaccination is recommended for cattle and bison in infected areas. This vaccine is associated with infections in veterinarians and other accredited animal health-care personnel after exposure CDC (1998). The CDC has established a registry of human exposures to the RB51 vaccine strain as a means to track its utilization.

Associated Disorders

Brucellosis is a multisystem disease and may present with a wide spectrum of clinical manifestations Sauret and Vilessova (2002). The incubation period ranges from 2 to 3 weeks, but may be as short as one week or as long as 3 months. Generalized symptoms, such as fever, night sweats, headache, weakness, arthralgia, and weight loss, are common in most cases. The name undulant fever is synonymous with brucellosis because of periodic fevers that may occur over weeks, months, or even years. Fever tends to occur in the evening or night, with normal body temperatures during the day. In some patients, acute and chronic brucellosis may lead to complications that can affect several organ systems.

Etiology

As the infective dose for *Brucella* species is low (<10 organisms), the handling of specimens and cultures requires special laboratory containment facilities to prevent exposure U. S. Department of Health and Human Services (1999). Many cases of laboratory acquired infections caused by *Brucella* species have been reported Martin-Mazuelos et al (1994). Laboratories that have the special practices, safety equipment, and facilities
necessary to handle *Brucella* species are referred to as Biosafety Level 3 (BSL-3) containment labs. Most clinical diagnostic laboratories do not have the containment facilities necessary to perform confirmation testing, although they can do primary cultures to recognize suspicious isolates. In clinical practice, *Brucella* species are most commonly isolated from blood and bone marrow specimens because there is infection of the reticuloendothelial system. On culture, *Brucella* species are facultative small, gram-negative coccobacilli, which grow only on an enriched laboratory medium such as chocolate agar (referred to as a fastidious organism). They frequently require 5 or more days of incubation to detect. The fastidious nature of the organism, and the requirement for prolonged incubation, limits success in detecting the organism in clinical samples. Serological testing, therefore, is the primary method for diagnosing brucellosis Young (1991), Nielsen (2002). The laboratory criterion for a probable diagnosis of brucellosis is 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 CDC (1997). Confirmation of brucellosis is by isolation of *Brucella* species from a clinical specimen or a four-fold or greater rise in *Brucella* agglutination titer between acute and convalescent phase serum specimens obtained greater than, or equal to, 2 weeks apart and studied at the same laboratory, or demonstration by immunofluorescence of *Brucella* spp. in a clinical specimen. Identification of *Brucella* species from culture is accomplished on the basis of biochemical tests, growth in the presence of thionin and basic fuchsin dyes, and agglutination in specific antisera Koneman et al (1997). Separation of the three main species into biovars is accomplished for epidemiological reasons using a combination of biochemical tests and agglutination reagents. Numerous PCR-based assays are used for the identification of *Brucella* to improve diagnostic capabilities, including procedures designed for the direct analysis of a variety of clinical specimens Matar et al (1996), Bricker (2002). These procedures, however, require further testing before they are available for clinical use. Testing is available through the state Public Health Laboratories by access to reagents through the CDC Laboratory Response Network. Numerous platforms of serological assays are used to detect antibody to *Brucella* spp.

**Epidemiology**

Brucellosis is a zoonosis, a disease that humans acquire from infected animals or from infected animal products. A variety of wild and domestic animals may be infected with the brucellae. The disease is maintained within animals by the association of susceptible animals to direct contact with infected animals or with an environment contaminated with discharges from infected animals. Aborted fetuses, placental membrane or fluids, and other vaginal discharges present after an infected animal has aborted or calved are all highly contaminated with infectious disease causing organisms Borbel (1997). Additionally, brucellosis may be carried from one herd to another by an infected or exposed animal. The mode of transmission occurs when a herd owner buys replacement cattle or bison that are infected or have been exposed to infection prior to purchase. The disease may also spread when wild animals, or animals from an affected herd, mingle with brucellosis-free herds. As more than 50 percent of the bison in Yellowstone National Park test positive for brucellosis, there is concern that those that leave the park may transmit the disease to elk and other animals in surrounding areas. Humans are generally infected by eating or drinking something that is contaminated with *Brucella*, inhaling the organisms, or having the bacteria enter the body through skin wounds Sauret and Vilessova (2002). The most common way to be infected is by eating or drinking contaminated milk products. If the milk is not pasteurized, the bacteria are transmitted to those who drink the milk or eat
Inhalation of Brucella organism is an uncommon route of infection, but can be a significant hazard for those in certain occupations, such as laboratory workers where the organisms are cultured. Inhalation is often responsible for a significant percentage of cases in abattoir employees and is a terrorist concern. Contamination of skin wounds may be a problem for people working in slaughterhouses or meat packing plants, or for veterinarians. Hunters may be infected through skin wounds or by accidentally ingesting the bacteria after cleaning deer, elk, moose, or wild pigs. There is no cure for brucellosis in animals, and human-to-human transmission is rare.

Pathophysiology

Factors contributing to the pathogenesis of Brucella species are not well defined and are currently undergoing investigation. Brucella species are facultative intracellular organisms and the disease spectrum is partially explained by the ability of this organism to evade host defense mechanisms by virtue of its intracellular location. Once in the host, the organisms are phagocytosed but are able to survive within these cells. They are carried into the lymph nodes and the bloodstream and become sequestered in various parts of the reticuloendothelial system. The intracellular organisms are released at these sites, are endocytosed by macrophages and monocytes, and continue a cycle of release and multiplication. It is hypothesized that the undulant fever pattern corresponds with the periodic release of bacteria and bacterial components from phagocytic cells. Relapses and recurrences of brucellosis are minimized to some degree by a balance between the virulence of the organism and the presence of an intact, functional cellular immune response. Life-long immunity is generally achieved after natural infection.

Signs and Symptoms

Brucelosis infection may not be obvious, requiring clinical suspicion in most cases to make the diagnosis. To support a diagnosis, a history of exposure to animal or animal products in an endemic area is important. Due to the insidious nature of the disease, there is no effective way to detect infected animals by their appearance. The most obvious sign in pregnant animals is abortion or birth of weak calves. Surveillance procedures are used to locate infection without testing each animal in every herd. Milk from dairy herds is checked two to four times a year by testing a small sample obtained from creameries or farm milk taken for evidence of brucellosis. Bison and cattle herds that do not produce milk for sale are routinely checked for brucellosis by blood-testing animals sold from these herds. Follow-up testing of herds is warranted when a positive sample is detected.

Standard Therapies

The primary goals of brucellosis therapy are to reduce the symptoms, and prevent complications and relapses. Therapy should be based on the location of the disease and the underlying condition of the patient. The treatment of human brucellosis is controversial because of the spectrum of the disease, the possibility of chronic infection, and the development of complications. Traditionally, a 6-week regimen of oral tetracycline combined with daily intramuscular streptomycin for 2 to 3 weeks is the preferred therapy for brucellosis. Standardized antimicrobial susceptibility testing is not performed for Brucella species.
**Agent Name Discussion**

<table>
<thead>
<tr>
<th>Agent Name</th>
<th>Discussion</th>
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<tbody>
<tr>
<td><strong>Doxycycline</strong></td>
<td>For adults, doxycycline is given orally for 45 days in combination with either streptomycin (i.m.) or gentamicin (i.v.). Doxycycline is not used in children under 8 years or age or in pregnant women.</td>
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<tr>
<td><strong>Streptomycin</strong></td>
<td>For adults, streptomycin is administered for 14 days in combination with oral doxycycline.</td>
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<tr>
<td><strong>Gentamicin</strong></td>
<td>For adults, gentamicin is administered in combination with oral doxycycline.</td>
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<tr>
<td><strong>Rifampin</strong></td>
<td>Rifampin is considered the drug of choice for children under 8 years of age and for pregnant women. It is given in combination with trimethoprim/sulfamethoxazole or gentamicin.</td>
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<tr>
<td><strong>Fluoroquinolones</strong></td>
<td>Gatefloxacin (400 mg i.v. every 24 hrs for 4 to 6 weeks), levofloxacin (500 mg i.v. every 24 hrs for 4 to 6 weeks), or moxifloxacin (44 mg i.v every 24 hrs for 4 to 6 weeks) are recommended.</td>
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**Animal Models**

Mouse models are used to access pathogenicity and virulence of genetically engineered strains of bacteria, to identify protective antigens, and to discover new virulence factors Cloeckaert et al (2002), Ko and Splitter (2003).

**Other Information – Web Sites**

This site contains information about brucellosis for the general public and for laboratory and health professionals. From the Public Health Response and Preparedness, CDC, [http://www.bt.cdc.gov/agent/brucellosis/index.asp](http://www.bt.cdc.gov/agent/brucellosis/index.asp)

The bioterrorism section of this website is a collaboration between IDSA and the Center for Infectious Disease Research and Policy at the University of Minnesota with funding from the Centers for Disease Control and Prevention (CDC) and Pharmacia.[http://www.idsociety.org/BT/ToC.htm](http://www.idsociety.org/BT/ToC.htm)

The Public Health Image Library was created by the CDC as a gateway to its pictures. This material is available to the public for reference, teaching, presentations, and public health messages. Use the PHIL search to find images pertaining to brucellosis. [http://phil.cdc.gov/Phil/results.asp](http://phil.cdc.gov/Phil/results.asp)

This USDA site contains information about brucellosis and the Yellowstone bison.[www.aphis.usda.gov/vs/nahps/brucellosis/cattle.htm](http://www.aphis.usda.gov/vs/nahps/brucellosis/cattle.htm)


In the unlikely event of a bioterrorism-related exposure to *Brucella* species, prophylactic therapy might be given prior to the onset of symptoms. This would most likely entail the use of oral antibiotics Sauret and Vilissova (2002).

**Journal Citations**


CDC 1997 Case definitions for infectious conditions under public health surveillance. *MMWR*, 46(RR10).


**Book Citations**


**Further Reading**