BRUCELLOSIS

AUGUST 2005

Outline

By law, health care providers must report suspected or confirmed Brucellosis to the local health department immediately (within 1 hr).

Even a single case of Brucellosis is considered an outbreak and is a public health emergency.

To report: call SFDPH communicable disease control (24/7 Tel: 415-554-2830).

Upon receipt, SFDPH will initiate the public health response and can facilitate lab testing.

AGENT

Brucellosis is a zoonotic disease of domestic and wild animals, caused by the non-motile, non-sporulating, small, gram-negative coccobacilli bacteria of the genus *Brucella.* Four species can be pathogenic in humans: *B. melitensis, B. abortus, B. canis* and *B. suis*. They are highly infectious, especially *B. melitensis* and *B. suis*.

Brucellae contain lipopolysaccharide (LPS) in the outer cell membrane, however this LPS is structurally different from that of the Enterobacteriaceae, and this feature may underlie the reduced pyrogenicity (less than 1/100th) of *Brucella* LPS compared with *E. coli* LPS.

EPIDEMIOLOGY

Brucellosis as a Biological Weapon

The US military developed *B. suis* as a biological weapon in the 1950's, but terminated this program in 1967. Their transmissibility by aerosol suggests that *Brucella* organisms might be a candidate for use as a bioweapon. Fewer than 100 organisms could constitute an infectious aerosol. The CDC considers brucellosis a lesser threat than agents such as anthrax and smallpox: its incubation period is rather long, many infections are asymptomatic, and the mortality is low. However, it might be used as an incapacitating agent as it often causes a protracted illness.

The most likely form of intentional release would be via infectious aerosols; however food-borne exposure is also possible. Any large-scale outbreak of brucellosis would suggest deliberate release of *Brucella* organisms. Bioterrorism might also be suggested by clusters of brucellosis cases without a travel history to endemic areas, without relevant foodborne or occupational exposures, or where the cases are linked in time and place (e.g. geographically related cases following a wind direction pattern).

Naturally Occurring Brucellosis

Brucella species infect mainly ruminant mammals, including cattle, sheep, goats, pigs, and camels, in which they cause genital infection, abortion, and fetal death. Additional animal reservoirs include elk, caribou, bison, deer, and wild and domestic canines. Animals may transmit *Brucella* organisms during septic abortion, at the time of slaughter, and in their milk. Humans are usually infected incidentally in one of three ways:

- Direct contact with the tissues of infected animals. Occupational exposures include those of veterinarians, shepherds, ranchers, and slaughterhouse workers, who are believed to become infected through skin abrasions, cuts, or conjunctival exposure.

- Ingestion of contaminated food or water. Consumption of contaminated milk products is the most common mode of acquisition worldwide. Pasteurization of dairy products prevents transmission and has drastically reduced the incidence of brucellosis in the developed world. Meat products are rarely the source of infection because they are not usually eaten raw and the number of organisms in muscle tissue is low.

- Inhalation of infectious aerosols. The inhalational route is of consequence for occupational exposures listed above, particularly slaughterhouse workers, and may also constitute a risk factor for laboratory workers who culture *Brucella* bacteria.

Naturally occurring exposures to brucellosis are unusual in the USA and tend to be isolated. Fewer than 200 total cases per year are reported in the United States, most of these in Texas and California. During the period 1994-2003 there were 275 total cases reported in California; of these, 2 occurred in San Francisco. The epidemiology of brucellosis in Texas and California has changed from a disease associated with exposure to cattle to one linked to the ingestion of unpasteurized goat milk products ("queso fresco") imported from Mexico.

Disease incidence is much higher in the Middle East and Mediterranean regions, and in China, India, and Latin America.

CLINICAL FEATURES

The brucellae are facultative intracellular pathogens that can survive and multiply within the phagocytic cells of the host. After entering the human body and being taken up by local tissue lymphocytes, brucellae are transferred through regional lymph nodes into the circulation and are subsequently seeded throughout the body, with tropism for the reticuloendothelial system.

Clinical manifestations of brucellosis are diverse and often non-specific, and the course of the disease is variable. For most exposures, the clinical syndrome does not clearly relate to the portal of entry of the organism; however those exposed via the aerosol route may have increased frequency of respiratory symptoms. *B. melitensis* tends to cause more severe, systemic illness than the other brucellae; *B. suis* is more likely to cause localized, suppurative disease.

BRUCELLOSIS: CLINICAL FEATURES	
Incubation Period	2-4 weeks (range 5 days to several months)
Signs & Symptoms	• Fever always occurs; spiking or "undulant" pattern may be apparent • May have acute, subacute, or chronic presentation • Other consitutional symptoms: malaise, anorexia, back pain, myalgias, arthralgias, headache • "Malodorous perspiration" • Mild lymphadenopathy (10-20%) • Hepatomegaly or splenomegaly (20-30%) • Nonspecific skin lesions (papules, ulcers, e. nodosum, petechiae) in 5% • Weight loss among chronically infected • Almost any organ system can be involved • Most affected persons recover in 3-12 months, however a minority may develop one or more of the complications below
Complications	• Skeletal: osteomyelitis (most common); also sacroiliitis, spondylitis, peripheral arthritis • Reproductive: spontaneous abortion; epididymo-orchitis • GI: acute ileitis, hepatitis, liver abscess, liver granuloma • CNS: meningitis, encephalitis, brain abscess, myelitis • CV: endocarditis, pericarditis • Pulmonary: bronchitis, pneumonia, lung nodules, abscess, hilar adenopathy, pleural effusion/empyema, lung abscess • Uveitis
Laboratory Findings	• Mild leukopenia with relative lymphocytosis • Mild anemia and thrombocytopenia may be present; DIC is rare • Other abnormalities are related to the organ system involved

DIFFERENTIAL DIAGNOSIS

Due to the non-specific presentation and numerous, varied complications of brucellosis in humans, the differential diagnosis is vast and will not be addressed in detail here. A high index of suspicion is necessary to diagnose brucellosis, due both to the non-specific presentation and to the relatively long latency period between inoculation and the development of symptoms.

Key clinical questions that help to suggest naturally-acquired brucella infection include:

- History of contact with ruminant mammals, via occupational or recreational exposures (veterinarians, slaughterhouse workers, ranchers, shepherds, laboratory workers, visitors to dairy farms or petting zoos)
- Consumption of unpasteurized milk products (e.g. "queso fresco")
- Travel to areas where brucellae are established in the animal population

In the setting of intentional attack using brucella, these exposures may be notably absent.

LABORATORY DIAGNOSIS

Definitive diagnosis of brucellosis is made when brucellae are recovered from infected tissues, typically blood or bone marrow. The rate of isolation ranges from 15-70%. The organism has also been recovered from urine, CSF, synovial fluid, and biopsies of liver and lymph nodes. *Brucella* species often require several weeks to grow in culture, so this method is not useful for rapid identification.

If you are testing or considering testing for Brucellosis, you should:

- **IMMEDIATELY notify SFDPH Communicable Disease Control (24/7 Tel: 415-554-2830)**
- **Notify the lab that Brucellosis is suspected, as the organism may pose a risk to personnel.**

Neither CDC nor the Working Group on Civilian Biodefense has issued bioterrorism-specific treatment/prophylaxis recommendations for Brucellosis. SFDPH will provide situational guidance in response to events (www.sfdph.org/cdcp).

A presumptive diagnosis can be made using specific antibody titers. The serum agglutination test (SAT) is based on antibody against lipopolysaccharide. Most cases of active infection have a single titer of 1:160 or higher. Drawbacks of the SAT include the inability to diagnose *B. canis* infection, cross-reaction with other gram-negative organisms, and the lack of seroconversion in some cases. Also, SAT are not suitable for patient follow-up since titers can remain elevated for a prolonged period. The ELISA test for brucellosis relies on cytoplasmic antigens and is both more sensitive and more specific than SAT. However, like SAT, titers can remain elevated for prolonged periods. A number of variations of PCR tests are becoming available, but standardization is still lacking.

TREATMENT AND PROPHYLAXIS

Treatment

Generally accepted principles of brucellosis treatment are that the antibiotics used must penetrate macrophages, and that monotherapy has a higher rate of relapse compared with combined therapy regimens.

BICHAT, the European Commission's Task Force on Biological and Chemical Agent Threats, has recommended as first-line therapy: Doxycline 100 mg IV/PO twice daily, combined with **either** streptomycin 1 gm IM once or twice daily for up to 2 weeks; **OR** rifampin 600-900 mg PO daily for 6 weeks; **OR** gentamicin 5 mg/kg/day IV in 2 divided doses for up to 2 weeks. This regimen, dosage-adjusted to body weight, is also first-line treatment for children >8 years old. Treatment with trimethoprim-sulfamethoxazole (TMP-SMX) plus rifampin is recommended for pregnant women and for children <8 years of age. Quinolones have been used with success against Brucellae, while macrolide antibiotics are not effective. Complications of brucellosis are also ed with 2-drug regimens, while neurobrucellosis has generally been treated with 3 agents.

Relapses occur in about 10% of cases, usually during the first year after infection, and are often milder in severity than the initial disease. Relapse has been managed with a repeated course of the usual antibiotic regimens. Most cases of relapse are felt to be caused by inadequate treatment.

Post-Exposure Prophylaxis

There is little evidence to support the utility of post-exposure prophylaxis against brucellosis in humans. BICHAT has recommended a 3-6 week course of doxycycline **OR** TMP-SMX, with the addition of rifampin to either drug. **In the event of outbreak, SFDPH will provide updated, situational guidelines for prophylaxis (www.sfdph.org/cdcp).**

Vaccination

There is currently no licensed vaccine available for brucellosis. Some limited clinical data exist on a live, attenuated vaccine candidate, but licensing and production of this vaccine are not anticipated.

INFECTION CONTROL*

These recommendations are current as of this document date. SFDPH will provide periodic updates as needed and situational guidance in response to events (www.sfdph.org/cdcp).

Person-to-person transmission of brucellosis is extremely rare. **Standard Precautions** are considered adequate for patients with brucellosis.

Brucella is sensitive to exposure to heat and most disinfectants but can survive in the environment for up to two years under specific conditions, becoming a continuing threat to both humans and animals.

REFERENCES

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* For description of Precautions, see Chapter on Infection Control.

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