Brucellosis

Undulant Fever, Malta Fever, Mediterranean Fever, Enzootic Abortion, Epizootic Abortion, Contagious Abortion, Bang's Disease

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Importance

Brucellosis, a bacterial disease caused by members of the genus *Brucella*, is an important zoonosis and a significant cause of reproductive losses in animals. Brucellosis is usually caused by *Brucella abortus*

Brucella species vary in their geographic distribution. *B. abortus* is found worldwide in cattle-raising regions except in Japan, Canada, some European countries, Australia, New Zealand and Israel, where it has been eradicated. Eradication from domesticated herds is nearly complete in the U.S. *B. abortus* persists in wildlife hosts in some regions, including the Greater Yellowstone Area of North America. *B. melitensis* is particularly common in the Mediterranean. It also occurs in the Middle East and Central Asia, around the Arabian Gulf and in some countries of Central America. This organism has been reported from Africa and India, but it does not seem to be endemic in northern Europe, North America (except Mexico), Southeast Asia, Australia or New Zealand. *B. ovis* probably occurs in most sheep-raising regions of the world. It has been reported from Australia, New Zealand, North and South America, South Africa and many countries in Europe.

In the past, *B. suis* was found worldwide in swine-raising regions. This organism has been eradicated from domesticated pigs in the U.S., Canada, many European countries and other nations. However, it persists in wild and/ or feral swine populations in some areas, including the U.S., Europe and Queensland, Australia. Sporadic outbreaks are reported in domesticated herds or humans due to transmission from this source. *B. suis* continues to occur in domesticated herds in some countries of South and Central America (including Mexico) and Asia. *B. suis* biovars 1 and 3 are found worldwide, but other biovars have a limited geographic distribution. Biovar 2 occurs in wild boar in much of Europe. Biovar 4 (rangiferine brucellosis) is limited to the Arctic regions of North America and Russia including Siberia, Canada and Alaska. Biovar 5 (murine brucellosis) is found in the former USSR.

destroy *Brucella* on contaminated surfaces include 2.5% sodium hypochlorite, 2-3% caustic soda, 20% freshly slaked lime suspension, or 2% formaldehyde solution (all tested for one hour). Alkyl quaternary ammonium compounds are not recommended. Autoclaving (moist heat of 121°C for at least 15 minutes) can be used to destroy *Brucella* species on contaminated equipment. These organisms can also be inactivated by dry heat (160-170°C for at least 1 hour). Boiling for 10 minutes is usually effective for liquids. Xylene (1ml/liter) and calcium cyanamide (20 kg/m3) are reported to decontaminate liquid manure after 2 to 4 weeks. *Brucella* species can also be inactivated by gamma irradiation (e.g. in colostrum) and pasteurization. Their persistence in unpasteurized cheese is influenced by the type of fermentation and ripening time. The fermentation time necessary to ensure safety in ripened, fermented cheeses in unknown, but is estimated to be approximately three months. *Brucella* is reported to persist for weeks in ice cream and months in butter. This organism survives for very short periods in meat, unless it is frozen; in frozen meat, survival times of years have been reported.

Infections in Humans

Incubation Period

The incubation period is difficult to determine in humans but has been estimated at five days to three months. Most infections seem to become apparent within two weeks. Aerosolization of bacteria in biological weapons could result in a shorter incubation period.

smooth margins. When the plates are viewed in daylight through a transparent medium, these colonies are translucent and a pale honey color. From above, they are convex and pearly white. *B. ovis* and *B. canis* are rough (R) forms. The colonies are round, shiny and convex, but their rough nature can be seen by examining the colony with oblique illumination. Most *Brucella* species form colonies within a few days, but isolates from seals grow slowly and may take 7 to 10 days to become visible on selective media. *Brucella* isolates can be identified to the species and biovar level by phage typing and cultural, biochemical and serological characteristics. Care should be taken during identification, as marine mammal isolates are sometimes misidentified initially as terrestrial strains. Genetic techniques can also be used for biotyping.

Most human infections are diagnosed by serology. Tests used include serum agglutination, a modified Coombs' (antiglobulin) technique, ELISAs and immunoblotting (Western blotting). Serologic diagnosis is complicated by previous exposures and other factors; a definitive diagnosis usually requires a fourfold rise in titer. Immunostaining can sometimes demonstrate the presence of *Brucella* spp. in a clinical specimen. PCR techniques can also be used for diagnosis. Chronic brucellosis can be extremely difficult to diagnose, if the serologic results are equivocal and the organism cannot be cultured.

Treatment

Antibiotics are usually the mainstay of treatment; long-term treatment may be required. Some forms of localized disease, such as endocarditis, may require surgery.

Prevention

Human brucellosis is usually prevented by controlling the infection in animals. Pasteurization of dairy products is an important safety measure where this disease is endemic. Unpasteurized dairy products and raw or undercooked animal products (including bone marrow) should not be consumed.

Good hygiene and protective clothing/equipment are very important in preventing occupational exposure. Precautions should be taken to avoid contamination of the skin, as well as inhalation or accidental ingestion of organisms when assisting at a birth, performing a necropsy, or butchering an animal for consumption. Particular care should be taken when handling an aborted fetus or its membranes and fluids. Risky agricultural practices such as crushing the umbilical cord of newborn livestock with the teeth or skinning aborted fetuses should be avoided. The Strain 19 *B. abortus* vaccine and *B. melitensis* Rev-1 vaccine must be handled with caution to avoid accidental injection or exposure. Adverse events have also been reported with the *B. abortus* RB51 vaccine, although it is safer than Strain 19. Persistent infections with vaccine strains have occasionally been reported in vaccinated animals. These strains can be shed in the milk or aborted fetuses and can infect humans. Obstetricians should also take precautions when assisting at human births, particularly in regions where brucellosis is common. Recently, an obstetrician became infected by ingesting amniotic fluid and secretions from a congenitally infected infant. In the laboratory, *Brucella* spp. should be handled under biosafety level 3 conditions or higher. Human vaccines are not available.

Morbidity and Mortality

Brucellosis is usually an occupational disease; most cases occur in abattoir workers, veterinarians, hunters, farmers, reindeer/caribou herders and livestock producers. Brucellosis is also one of the most easily acquired laboratory infections. People who do not work with animals, tissues or bacterial cultures usually become infected by ingesting unpasteurized dairy products. Other cultural practices, such as eating bone marrow from reindeer and caribou infected with *B. suis*, are risk factors in some populations. In endemic areas, the reported incidence ranges from fewer than 0.01 to more than 200 cases per 100,000 population. Human brucellosis is rare in the U.S.; the annual incidence is less than 0.5 cases per 100,000 persons; approximately 100 cases have been reported annually for the past ten years. However, some studies suggest that this disease is underdiagnosed and underreported in the U.S.

Many human infections are asymptomatic or self-limiting; however, some symptomatic infections can be prolonged, with slow recovery and a small possibility of complications. Increased numbers of symptomatic infections could be seen after a biological attack with aerosolized bacteria. The incidence and severity of disease varies with the species of *Brucella*. *B. melitensis* is considered to be the most severe human pathogen in the genus. *B. abortus* and *B. suis* biovars 1, 3 and 4 are also important human pathogens. *B. suis* biovar 2 and *B. canis* infections are rarely reported in humans. However, serologic studies have reported antibodies to *B. canis* in 13% of hospital patients in Mexico, 0.3% of sera tested in Germany, 0.4% of US military populations, 0.6% of Florida residents and 68% of Oklahoma residents. As of July 2007, only four human infections with marine mammal *Brucella* have been reported. One infection occurred in a researcher exposed in the laboratory. Two patientd[dslow10(de)8(nl)4(t)-4(f)2( )]TJ0.002 Tc4741495 Tw 0 -1.15 T

Brucellosis is rarely fatal if treated; in untreated persons, estimates of the case fatality rate vary from less than 2% to 5%. Deaths are usually caused by endocarditis or meningitis.

Infections in Animals

Species Affected

Most species of *Brucella* are maintained in a limited number of reservoir hosts. Maintenance hosts for *Brucella abortus* include cattle, bison (*Bison* spp.) water buffalo (*Bubalus bubalus*), African buffalo (*Syncerus caffer*), elk and camels. A feral pig population was recently reported to maintain *B. abortus* in the U.S. Sheep and goats are the reservoir hosts for *B. melitensis*. Sheep are also the maintenance hosts for *B. ovis*. In addition, *B. ovis* occurs in farmed red deer (*Odocoileus virginianus*) in New Zealand. *B. canis* is maintained in dogs and *B. neotomae* in rodents. *B. suis* contains more diverse isolates than other *Brucella* species, and these isolates have broader host specificity. *B. suis* biovars 1, 2 and 3 affect swine. Biovars 1 and 3 are found in both domesticated pigs (*Sus scrofa domesticus*) and wild or feral pigs. Biovar 2 currently occurs mainly in wild boar (*Sus scrofa scrofa*) and European hares (*Lepus capensis*); however, this biovar can be transmitted from these reservoirs to domesticated pigs, and spreads readily in these herds. Biovar 4 is maintained in caribou and reindeer (*Rangifer tarandus* and its various subspecies). Biovar 5 is found in small rodents. Marine *Brucella* species have been found by culture or serology in many pinniped and cetacean species including seals, sea lions, walruses, porpoises, dolphins, [illegible]

Porcine and rangiferine brucellosis (B. suis)

In pigs, the most common symptom is abortion, which can occur at any time during gestation, and weak or stillborn piglets. Vaginal discharge is often minimal and abortions may be mistaken for infertility. Occasionally, some sows develop metritis. Temporary or permanent orchitis can be seen in boars. Boars can also excrete *B. suis* asymptomatically in the semen and sterility may be the only sign of infection. Swollen joints and tendon sheaths, accompanied by lameness and incoordination, can occur in both sexes. Less common signs include posterior paralysis, spondylitis and abscesses in various organs. Although some pigs recover, others remain permanently infected. Fertility can be permanently impaired, particularly in boars. Some animals remain asymptomatic.

In hares, *B. suis* biovar 2 infection is characterized by nodules in the internal organs, particularly the reproductive organs, as well as the subcutaneous tissues and muscles. The nodules can become purulent. The animal's body condition may be minimally affected.

In caribou and reindeer, *B. suis* biovar 4 can cause abortion and retained placenta. Metritis and mastitis can also occur. Males may develop orchitis. Lameness can occur in both sexes from arthritis, bursitis, tenosynovitis and/ or hygromas. Subcutaneous abscesses are also seen.

Canine brucellosis (B. canis)

B. canis can cause abortions and stillbirths in pregnant dogs. Most abortions occur late, particularly during the seventh to ninth week of gestation. Abortions

edema and bloodstained fluid in the body cavities. In ruminant fetuses, the spleen and/or liver may be enlarged, and the lungs may exhibit pneumonia and fibrous pleuritis. Abortions caused by *Brucella* spp. are typically accompanied by placentitis. The cotyledons may be red, yellow, normal or necrotic. In cattle and small ruminants, the intercotyledonary region is typically leathery, with a wet appearance and focal thickening. There may be exudate on the surface.

In adults, granulomatous to purulent lesions may be found in the male and female reproductive tract, mammary gland, supramammary lymph nodes, other lymphoid tissues, bones, joints and other tissues and organs. Mild to severe endometritis may be seen after an abortion, and males can have unilateral or bilateral epididymitis and/or orchitis. In *B. abortus*-infected cattle, hygromas may be found on the knees, stifles, hock, angle of the haunch, and between the nuchal ligament and the primary thoracic spines.

In hares, *B. suis* biovar 2 infections are associated with nodules of varying sizes in internal organs, particularly the reproductive organs but also the spleen, liver, lung and most other organs. The skin and subcutaneous tissues can also be affected. These nodules often become purulent. Despite the nodules, the hare's body condition may be good.

Brucella ovis

In rams infected with *B. ovis*, lesions are usually limited to epididymitis and orchitis. Epididymal enlargement can be unilateral or bilateral, and the tail is affected more often than the head or body. Fibrous atrophy can occur in the testis. The tunica vaginalis is often thickened and fibrous, and can have extensive adhesions. Although placentitis is uncommon, it is occasionally seen in infected ewes.

Brucella canis

Aborted puppies are often partially autolyzed and have evidence of generalized bacterial infection. Fetal lesions can include subcutaneous edema, subcutaneous congestion and hemorrhages in the abdominal region, serosanguinous peritoneal fluid, and degenerative lesions in the liver, spleen, kidneys and intestines.

The lymph nodes are often enlarged in affected adults. The retropharyngeal and inguinal lymph nodes are often involved, but generalized lymphadenitis also occurs. The spleen is frequently enlarged, and may be firm and nodular. Hepatomegaly may also be seen. Scrotal edema, scrotal dermatitis, epididymitis, orchitis, prostatitis, testicular atrophy and fibrosis occur in some infected males, and metritis and vaginal discharge may be seen in females. Less commonly reported lesions include discospondylitis, meningitis, focal non-suppurative encephalitis, osteomyelitis, uveitis, and abscesses in various internal organs.

Brucella in marine mammals

In marine mammals, brucellosis has been linked to lesions in a few animals. Reported lesions include meningoencephalitis, subcutaneous abscesses, placentitis/abortion, epididymitis, chronic purulent or granulomatous orchitis, lymphadenitis, mastitis, spinal discospondylitis, peritonitis, a mineralized lung granuloma, hepatic abscesses, hepatic and splenic necrosis, and macrophage/histiocytic cell infiltration in the liver, spleen and lymph nodes. In dolphins with meningoencephalitis, the lesions were described as severe, chronic, widespread, nonsuppurative meningitis most severe in the brainstem. The meningitis was accompanied by periventricular encephalitis. *Brucella* has also been recovered from apparently normal tissues and animals with no lesions.

Diagnostic Tests

Brucellosis can be diagnosed by culture, serology or other tests.

Microscopic examination

Microscopic examination of smears stained with the Stamp's modification of the Ziehl-Neelsen method can be used for a presumptive diagnosis. Organisms may be found in abortion products, vaginal discharges, milk, semen or various tissues. *Brucell*a species are not truly acid-fast, but they are resistant to decolorization by weak acids, and stain red against a blue background. Brucellae are coccobacilli or short rods, usually arranged singly but sometimes in pairs or small groups. This test is not definitive. Other organisms such as *Chlamydophila abortus* and *Coxiella burnetii* can resemble *Brucella*. Direct examination may not detect the small numbers of organisms present in milk and dairy products.

Culture

Brucella species can be recovered from numerous tissues and secretions, particularly fetal membranes, vaginal secretions, milk (or udder secretions in nonlactating cows), semen, arthritis or hygroma fluids, and the stomach contents, spleen and lung from aborted fetuses. Blood cultures are often used to detect

practiced in New Zealand and some other countries, but not in the U.S. Successful vaccines have been difficult to develop for pigs; this species is generally not vaccinated except in China. No vaccines are made for dogs. Vaccines have not been successful in preventing fistulous withers or poll evil in horses.

B. abortus, *B. melitensis* and *B. suis* can be eradicated from a herd by test-and-removal procedures, or by depopulation. Some swine programs are designed to retain desirable genetic characteristics in the herd. Good management can reduce the incidence of infection in an infected herd. Whenever possible, animals should give birth in individual pens. Transmission is reduced by immediate disposal of the placenta, contaminated bedding and other infectious material, followed by thorough cleaning and disinfection. The prevalence of *B. ovis* can be decreased by examining rams before the breeding season and culling rams with palpable abnormalities. However, palpable lesions are not found in all infected rams, and laboratory testing of rams should also be considered. Test-and-removal methods directed at rams can eradicate this organism from a flock. *B.-ovis*-free infections in ewes are generally prevented by controlling infections in rams. Infections in other species are generally prevented by controlling *Brucella* species in their maintenance hosts.

Nationwide eradication programs for *B. abortus*, *B. melitensis* and *B. suis* include quarantines of infected herds, vaccination, test-and-slaughter and/or depopulation techniques, cleaning and disinfection of infected farms, various forms of surveillance and tracebacks. *B. ovis* has been eradicated from sheep in the Falkland Islands by test-and-removal methods directed at rams. In areas where a *Brucella* species is not endemic, infected herds are usually quarantined and the animals are euthanized. In the U.S., *B. suis* has been eradicated from commercial swine, and *B. abortus* has nearly been eradicated from domesticated ruminants. Various control methods are being directed at wild animal reservoirs including wild bison and elk herds in the Greater Yellowstone Area, and s -2(fec(B. wal swi4 ǐ,[(reserv)3era)6 0 -1.144 T([(0 Td(B -1.152 Tland)-4(,

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