194e Brucellosis

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DEFINITION

Brucellosis is a bacterial zoonosis transmitted directly or indirectly to humans from infected animals, predominantly domesticated ruminants and swine. The disease is known colloquially as *undulant fever* because of its remittent character. Although brucellosis commonly presents as an acute febrile illness, its clinical manifestations vary widely, and definitive signs indicative of the diagnosis may be lacking. Thus the clinical diagnosis usually must be supported by the results of bacteriologic and/or serologic tests.

ETIOLOGIC AGENTS

Human brucellosis is caused by strains of *Brucella*, a bacterial genus that was previously suggested, on genetic grounds, to comprise a single species, *B. melitensis*, with a number of biologic variants exhibiting particular host preferences. This view was challenged on the basis of detailed differences in chromosomal structure and host preference. The traditional classification into nomen species is now favored both because of these differences and because this classification scheme closely reflects the epidemiologic patterns of the infection. The nomen system recognizes *B. melitensis*, which is the most common cause of symptomatic disease in humans and for which the main sources are sheep, goats, and camels; *B. abortus*, which is usually acquired from cattle or buffalo; *B. suis*, which generally is acquired from swine but has one variant enzootic in reindeer and caribou and another in rodents; and *B. canis*, which is acquired most often from dogs. *B. ovis*, which causes reproductive disease in sheep, and *B. neotomae*, which is specific for desert rodents, have not been clearly implicated in human disease. Two new species, *B. ceti* and *B. pinnipedialis*, have recently been identified in marine mammals, including seals and dolphins. At least one case of laboratory-acquired human disease due to one of these species has been described, and apparent cases of natural human infection have been reported. As infections in marine mammals appear to be widespread, more cases of zoonotic infection in humans may be identified. Other newly reported species include *B. microti* (isolated from field voles) and *B. inopinata* (isolated from a patient with a breast implant). Additional novel strains have been described from diverse species, including baboons, foxes, frogs, and various rodents, and the genus likely will expand further in forthcoming years. Moreover, it has become apparent that *Brucella* is closely related to the genus *Ochrobactrum*, which includes environmental bacteria sometimes associated with opportunistic infections. Genomics-based studies are beginning to elucidate the pathway of evolution from free-living soil bacteria to highly successful intracellular pathogens.

All brucellae are small, gram-negative, unencapsulated, nonsporulating, nonmotile rods or coccobacilli. They grow aerobically on peptone-based medium incubated at 37°C; the growth of some types is improved by supplementary CO_2. In vivo, brucellae behave as facultative intracellular parasites. The organisms are sensitive to sunlight, ionizing radiation, and moderate heat; they are killed by boiling and pasteurization but are resistant to freezing and drying. Their resistance to drying renders brucellae stable in aerosol form, facilitating airborne transmission. The organisms can survive for up to 2 months in soft cheeses made from goat's or sheep's milk; for at least 6 weeks in dry soil contaminated with infected urine, vaginal discharge, or placental or fetal tissues; and for at least 6 months in damp soil or liquid manure kept under cool dark conditions. Brucellae are easily killed by a wide range of common disinfectants used under optimal conditions but are likely to be much more resistant at low temperatures or in the presence of heavy organic contamination.

EPIDEMIOLOGY

Brucellosis is a zoonosis whose occurrence and control are closely related to its prevalence in domesticated animals. Its distribution is worldwide apart from the few countries where it has been eradicated from the animal reservoir. The true global prevalence of human brucellosis is unknown because of the imprecision of diagnosis and the inadequacy of reporting and surveillance systems in many countries. Recently, there has been increased recognition of the high incidence of brucellosis in India and parts of China and of importations to countries in Oceania, such as Fiji. In Europe, the incidence of brucellosis in a country is inversely related to gross domestic product, and, in both developed and less well-resourced settings, human brucellosis is related to rural poverty and inadequate access to medical care. Failure of veterinary control programs due to conflict or for economic reasons contributes further to the emergence and re-emergence of disease, as seen currently in some eastern Mediterranean countries.

Even in well-resourced settings, the true incidence of brucellosis in domesticated animals may be 10–20 times higher than the reported figures. Bovine brucellosis has been the target of control programs in many parts of the world and has been eradicated from the cattle populations of Australia, New Zealand, Bulgaria, Canada, Cyprus, Great Britain (including the Channel Islands), Japan, Luxembourg, Romania, the Scandinavian countries, Switzerland, and the Czech and Slovak Republics, among other nations. Its incidence has been reduced to a low level in the United States and most Western European countries, with a varied picture in other parts of the world. Efforts to eradicate *B. melitensis* infection from sheep and goat populations have been much less successful. These efforts have relied heavily on vaccination programs, which have tended to fluctuate with changing economic and political conditions. In some countries (e.g., Israel), *B. melitensis* has caused serious outbreaks in cattle. Infections with *B. melitensis* still pose a major public health problem in Mediterranean countries; in western, central, and southern Asia; and in parts of Africa and South and Central America.

Human brucellosis is usually associated with occupational or domestic exposure to infected animals or their products. Farmers, shepherds, goatherds, veterinarians, and employees in slaughterhouses and meat-processing plants in endemic areas are occupationally exposed to infection. Family members of individuals involved in animal husbandry may be at risk, although it is often difficult to differentiate food-borne infection from environmental contamination under these circumstances. Laboratory workers who handle cultures or infected samples also are at risk. Travelers and urban residents usually acquire the infection through consumption of contaminated foods. In countries that have eradicated the disease, new cases are most commonly acquired abroad. Dairy products, especially soft cheeses, unpasteurized milk, and ice cream, are the most frequently implicated sources of infection; raw meat and bone marrow may be sources under exceptional circumstances. Infections acquired through cosmetic treatments using materials of fetal origin have been reported. Person-to-person transmission is extremely rare, as is transfer of infection by blood or tissue donation. Although brucellosis is a chronic intracellular infection, there is no evidence for increased prevalence or severity among individuals with HIV infection or with immunodeficiency or immunosuppression of other etiologies.

Brucellosis may be acquired by ingestion, inhalation, or mucosal or percutaneous exposure. Accidental injection of the live vaccine strains of *B. abortus* (S19 and RB51) and *B. melitensis* (Rev 1) can cause disease. *B. melitensis* and *B. suis* have historically been developed as biological weapons by several countries and could be exploited for bioterrorism (Chap. 261e). This possibility should be borne in mind in the event of sudden unexplained outbreaks.

IMMUNITY AND PATHOGENESIS

Exposure to brucellosis elicits both humoral and cell-mediated immune responses. The mechanisms of protective immunity against human brucellosis are presumed to be similar to those documented in laboratory animals, but such generalizations must be interpreted with caution. The response to infection and its outcome are influenced by the virulence, phase, and species of the infecting strain. Differences have been reported between *B. abortus* and *B. suis* in modes of cellular entry and subsequent compartmentalization and processing.