Brucellosis

Author: Prof Jacques Godfroid


Licensed under a Creative Commons Attribution license.

PATHOGENESIS

Smooth Brucella spp. (B. abortus, B. melitensis, B. suis)

Brucella spp. readily penetrate mucous membranes, such as those of the pharynx and alimentary tract, and survives and multiplies particularly in cells of the mononuclear phagocytic system. After penetration, the organisms are phagocytosed by neutrophils and macrophages which carry them to the regional lymph nodes where they multiply and induce a lymphadenitis which may persist for months. Multiplication of the organism here may be followed by a bacteraemia which may persist for several months, resolve itself, or be recurrent for at least two years in five to ten per cent of animals. Recurrence occurs particularly during pregnancy. During the bacteraemic phase, organisms are carried intracellularly in neutrophils and macrophages, or free in the plasma and localize in various organs, especially the gravid uterus, udder and supramammary lymph nodes. Localization may also occur in other lymph nodes and the spleen, and in bulls in the testes, and male accessory sex glands. Occasionally bacterial localization occurs in synovial structures causing a purulent tendovaginitis, arthritis or bursitis.

Localization of the infection in the endometrium of the gravid uterus and in foetal membranes of cattle appears to be the result of the special affinity of the organism for erythritol, elevated levels of which occur in the placenta and fetal fluids from about the fifth month of gestation. The chorionic epithelium becomes colonized and infection extends to the placental stroma, blood vessels and ultimately, to the foetus. There is considerable variation in the uterine and placental lesions in both natural and experimental Brucella spp. infections and foetuses that become infected late in gestation may be aborted without any grossly recognizable placental lesions. Depending on the severity of the placentitis, abortion, premature birth or the birth of a viable or non-viable calf may result. The abundance of erythritol in the pregnant uterus results in the massive multiplication of Brucella organisms in this organ. In the pregnant animal, Brucella spp. replicate in the placental trophoblast during middle and late gestation after the cells have actively begun secreting steroids. The mechanism leading to abortion after mid gestation in brucellosis is not known. Infected trophoblasts produce cortisol, a steroid hormone not produced in the non-infected placenta. This production, coupled with increased levels of oestrogen and prostaglandin synthesis and
Livestock Health, Management and Production › High Impact Diseases › Contagious Diseases › Brucellosis

decreased production of progesterone, mimics the hormonal changes occurring at term in non-Brucella infected cattle and leads to the initiation of parturition.

Up to 35% of cows may be resistant to infection with *B. abortus* because their macrophages have a greater ability to kill *B. abortus*. The level of macrophage function which is reduced in susceptible cows plays a role in the establishment of chronic infections. This enhanced macrophage killing activity is significantly greater in cows that are genetically resistant to infection including that caused by *Mycobacterium bovis*, *Salmonella* Dublin and *Salmonella* Typhimurium as well as *B. abortus*. The bovine *nramp1* gene, the homologue of the murine tuberculosis resistance gene, has been identified as a major candidate for controlling the *in vivo* resistant phenotype to *Brucella* infection. It has been demonstrated in a murine macrophage cell line transfected with the resistance- and susceptibility-associated alleles of the bovine *nramp1* gene, that these alleles critically affect the control of the replication of *B. abortus*.

Phagocytes have developed antimicrobial defense mechanisms such as oxidative burst, acidification of phagosomes, or fusion of phagosomes with lysosomes, to eliminate pathogens, while on the other, facultative intracellular bacteria have developed strategies counteracting the host cell defenses, resulting in intramacrophagic survival. Recent studies have revealed that caveolae or lipid rafts anchored in the membrane of macrophages are implicated in the entry of *Brucella* spp. into murine macrophages and mediate an endocytic pathway avoiding fusion with lysosomes. It has been shown that human macrophage phagosomes rapidly acidify to a pH of 4.0–4.5 following *Brucella suis* infection and that this early acidification is crucial for intracellular replication as neutralization results in bacterial elimination. In addition, if the phagosomal membrane is disrupted, then *B. suis* fails to multiply intracellularly. These results highlight the necessity of an intact, acidic phagosome as a predominant replicative niche for *Brucella* spp. in macrophages; it is called the “brucellosome”. A series of genes are involved in the adaptation of *Brucella* spp. to three major stress conditions within the phagosome, i.e. acid stress, starvation and low oxygen tension.

Long-term residence of *Brucella* spp. in the phagosomal compartment of host macrophages is essential for their ability to produce disease in both natural and experimental hosts. *Brucella* spp. infections inhibit spontaneously occurring apoptosis in human monocytes, thus preventing host cell elimination. This might represent a strategy for the persistence of *Brucella* spp. in infected hosts. Studies with *Brucella* mutants suggest that stationary-phase physiology is critical for their successful long-term residence in host macrophages, and reveal striking parallels between the strategies employed by rhizobiae to establish and maintain intracellular residence in their plant host and those used by the *Brucella* spp. during their long-term survival in the phagosomal compartment of host macrophages.

Cytokines such as IFN-gamma, TNF-alpha, IL-2, IL-10 and IL-12 control the intracellular growth of *Brucella* spp. Amongst these cytokines, the most important is IFN-gamma which strongly activates macrophages and induces an enhanced intracellular killing of *Brucella* spp. In non-phagocytic cells, such as Hela epithelial cells, the *Brucella* bacterium initially interacts with compartments of the early endocytic cascade, then rapidly segregates from this intracellular pathway and associates with the autophagocytic cascade. During the late stages of infection, *Brucella* spp. proliferate within the endoplasmic reticulum of
host cells. They replicate extensively without inducing obvious damage to the infected cell, and therefore seem to promote the survival of the cells for their own benefit. Eventually, in the bovine pregnant uterus, this extensive replication does lead to cell necrosis and acute inflammation and to the release of huge numbers of bacterial cells from both the trophoblasts and foetal tissues.

**Brucella ovis**

Rams become infected after penetration by *B. ovis* of the mucous membranes of the prepuce, penis, nasal cavity or conjunctiva. This is followed by bacteraemia and localization of the infection in lymph nodes and organs such as the epididymis, ampullae, seminal vesicles, bulbo-urethral glands, spleen, liver and kidneys. Organisms are first excreted in the semen from between 31 and 45 days following exposure.

Gross lesions only develop in the genitalia. In rams the earliest lesions usually occur in the tail of the epididymis, but lesions in the head and/or body of the epididymis may develop later. Initially the bacteria cause degeneration and necrosis of the epididymal epithelium, resulting in leakage of semen into the interstitial tissues where it provokes a severe inflammatory reaction and the development of spermatic granulomas. Similar inflammatory changes may also occur in the vas deferens, ampullae, seminal vesicles, bulbo-urethral glands and testes.

Inflammatory cells (particularly neutrophils) in semen, and a decrease in the production and quality of sperm as a consequence of testicular degeneration, all lead to lower fertility or infertility. Infertility may also be caused by the total cessation of spermatogenesis or by obstruction of the epididymis by spermatic granulomas and the development of a spermatocoele. There is a direct relationship between the semen quality, extent of the epididymal lesions and the number of leukocytes present in the semen. The reduction in fertility is ascribed to both low spermatozoa counts and the high number of defective spermatozoa; defects of the spermatozoal head and neck being common.

In ewes organisms enter mainly through the vaginal mucosa. In pregnant ewes, the ensuing bacteraemia causes a placentitis that may result in abortion or the birth of lambs with reduced birth weights. However, despite induction of severe endometritis, *B. ovis* has a relatively low capacity to induce abortion in sheep. After experimental infection, the uterus and the iliac and supramammary lymph nodes are the main target organs of *B. ovis* infection in ewes.