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Lecture title: BRUCELLOSIS ASSOCIATED WITH *BRUCELLA ABORTUS*

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Summary:

(BANG'S DISEASE)

ETIOLOGY

Brucella abortus,* a gram-negative, facultative intracellular coccobacillus of the family Brucellaceae,** is the organism responsible for bovine brucellosis. *B. abortus* is one of 10 species with validly published names, including *B. melitensis, B. abortus, B. suis, B. ovis, B. neotomae, B. canis, B. ceti, B. pinnipedialis, B. microti,* and *B. inopinata,* each of which has specific host preferences. ***B. abortus is responsible for **bovine brucellosis**, ***B. melitensis*** is the main causative agent of brucellosis **in small ruminants and human**, ***B. suis*** for brucellosis in **swine**, and ***B. ovis* in sheep**.

EPIDEMIOLOGY:

Occurrence

Bovine brucellosis has a worldwide occurrence and, according to the Food and Agriculture Organization (FAO), the World Health Organization (WHO), and the World Organization for Animal Health (OIE), is still one of the **most important and widespread bacterial zoonosis in the world**. The prevalence of infection varies considerably among herds, areas, and countries. Many countries have made considerable progress with their eradication programs, and some have eradicated the disease. However, in other countries brucellosis is still a serious disease facing the veterinary and medical professions.

Cattle

Infection occurs in cattle of all ages but is most common in sexually mature animals, particularly dairy cattle. **Abortions are most common during outbreaks and primarily occur**

in unvaccinated heifers over 5 months pregnant. Bulls are affected with orchitis, epididymitis, and seminal vesiculitis.

Methods of Transmission:

Parturition/Abortion

The **risk posed to susceptible animals** following parturition or abortion of infected cattle depends on three factors:

- Number of organisms excreted
- Survival of these organisms under the existing environmental condition
- Probability of susceptible animals being exposed to enough organisms to establish infection

Transmission

-The disease is transmitted mainly by **ingestion, penetration of the intact skin and conjunctiva, and contamination of the udder during milking.**

- Consuming feedstuffs or water supplies contaminated by discharges and fetal membranes from infected cows, and contact with aborted fetuses as well as infected newborn calves are the most common methods of spreading the disease.

- Intra herd spread occurs by both vertical and horizontal transmission. **Horizontal transmission is usually by direct contamination** and also the possibility of introduction of infection by flies, dogs, rats, ticks, infected boots, fodder, and other inanimate objects exists.

-Evidence exists for horizontal, dog-to-dog, cattle-to-dog, dog-to-cattle, and dog-to-human transfer of infection.

- The most likely and effective means of cattle-to dog transfer is exposure to **aborted fetuses** or **infected placental membranes,** because dogs commonly ingest the products of parturition.

-Spread between herds movement of an infected animal from an infected herd to a susceptible non-infected herd is a common method of transmission.

- In the same way that the more common forms of **mastitis c**an be spread during milking, *B. abortus* infection can be spread from a cow whose milk contains the organism to an uninfected cow.

Bulls and Semen:

Bulls **do not usually transmit infection from infected to non-infected cows mechanically**. Infected bulls may discharge semen containing organisms but are unlikely to transmit the infection. The risk of spread from the bull is much higher, however, if the semen is used for artificial insemination.

Carrier Cows:

Few infected cows ever recover from infection completely and should be considered as permanent carriers whether or not abortion occurs.

- Excretion of the organism in the milk is usually intermittent, is more common during late lactation, and can persist for several years. **In cattle vaccinated before infection, the degree of excretion of *B. abortus* in the milk is less than in non-vaccinated animals.**

Animal Risk Factors:

-Susceptibility of cattle to ***B. abortus* infection is influenced by the age, sex, and reproductive status** of the individual animal. **Sexually mature, pregnant cattle are more susceptible to infection with the organism than sexually immature cattle of either sex**.

-**Natural exposure to field strains** occurs primarily at the **time of parturition of infected cows**. The greater the number of infected cows that abort or calve, the greater the exposure risk to the other cattle in the herd.

-**Young cattle are less susceptible to *B. abortus* than older, sexually mature cattle**. Susceptibility appears to be **more commonly associated with sexual maturity than age**.

-Young, sexually immature cattle generally do not become infected following exposure, or recover quickly.

- Susceptibility increases with pregnancy and as the stage of gestation increases.

Management Risk Factors:

The spread of the disease from one herd to another and from one area to another is almost always caused by the movement of an infected animal from an infected herd into a no infected susceptible herd.

Economic Importance:

- Losses in animal production caused by this disease can be of major importance, primarily because of **decreased milk production in aborting cows.**

- The common sequel of **infertility increases** the period between lactations, and in an infected herd **the average inter calving period may be prolonged by several months**. In addition to the loss of milk production, there is the loss of calves and interference with the breeding program.

- A high incidence of temporary and permanent infertility results in **heavy culling** of valuable cows, and some **deaths occur as a result of acute metritis** following **retention of the placenta**.

Zoonotic Implications:

According to the Food FAO, the WHO, and OIE, brucellosis is still one of the most important and widespread zoonosis in the world. Of the six *Brucella* spp. known to cause **human disease (*B. melitensis, B. abortus, B. suis, B. canis, B. ceti,* and *B. pinnipedialis*)**, ***B.melitensis* is the one with the largest public health** impact because it is the most virulent species and has the highest prevalence in small ruminant populations in many areas of the world. ***B. abortus* and *B. suis* serovars 1, 3, and 4 are also important human pathogens.** Most cases in humans are occupational and occur in **farmers, veterinarians, and slaughterhouse personnel after direct contact with infected animals or animal material contaminated with the pathogen.** The

organism can be isolated from many organs other than the udder and uterus, and the handling of a carcass of an infected animal may represent severe exposure. Infection can also occur after ingestion of raw milk or raw milk products. Officially approved methods of commercial pasteurization render naturally *Brucella*-contaminated raw milk safe for consumption.

PATHOGENESIS:

Following ingestion most commonly through the **digestive or respiratory tract** *Brucella* spp. can invade epithelial cells of the host, allowing infection though intact mucosal surfaces. Once invasion successfully occurs the organism may be phagocytized by host immune cells and may also invade non-phagocytic host cells through a mechanism that is not entirely understood. Following cell invasion the organism is contained in a membrane-bound modified phagosome, which is highly permissive for intracellular replication of *Brucella.*

Invaded polymorphonuclear leukocytes then transport the pathogen to regional lymph nodes, other sites **such as the reticuloendothelial system, and organs such as the udder and when present the fetal placenta**. In the draining lymph node, *Brucella* infection causes cell lysis and eventual lymph node hemorrhage 2 to 3 weeks following exposure. Because of vascular injury, some of the bacteria enter the bloodstream and subsequent **bacteremia** occurs, which disseminates the pathogen throughout the body. ***B. abortus*** has a **predilection** for

the **placenta; udder; testicle; and accessory male sex glands, lymph nodes, joint capsules, and bursae**.

Erythritol, a substance produced by the fetus and capable of stimulating the growth of *B. abortus*, occurs naturally in greatest concentration in the placental and fetal fluids and is responsible for localization of the infection in these tissues. Invasion of the gravid uterus results in a **severe ulcerative endometritis** of the intercotyledonary spaces. The allantochorion, fetal fluids, and placental cotyledons are invaded, and the villi are destroyed. The organism has a marked **predilection for the ruminant placenta.**

In **acute infections of pregnant cows**, up to 85% of the bacteria are in cotyledons, placental membranes, and allantoic fluid. The resulting **tissue necrosis of the fetal membranes allows transmission of the bacteria to the fetus.** The net effect of chorionic and fetal colonization is abortion during the last trimester of pregnancy.

Abortion occurs principally in the last 3 months of pregnancy, and the incubation period is inversely proportional to the stage of development of the fetus at the time of infection. **Congenital infection can occur in newborn calves as a result of in utero infection**, and the infection may persist in a small proportion of calves, which may also be serologically negative until after their first parturition or abortion.

- **In the adult, non-pregnant cow**, localization occurs in the udder, and the uterus, if it becomes gravid, is infected from periodic bacteremic phases originating in the udder. Infected udders are clinically normal, but they are important as a source of reinfection of the uterus, as a **source of infection** for calves or humans drinking the milk.

CLINICAL FINDINGS:

-Abortion The clinical findings are dependent on the immune status of the herd. In highly susceptible non-vaccinated pregnant cattle, abortion after the 5th month of pregnancy is a typical feature of the disease in cattle.

- **Retention of the placenta and metritis** are common **sequelae to abortion**.
- **Mixed infections** are usually the cause of the metritis, which may be acute, with **septicemia and death** following, or chronic, leading to **sterility.**

- **Orchitis and Epididymitis** in **bulls**, Orchitis and epididymitis occur occasionally. One or both scrotal sacs may be affected, with acute, **painful swelling to twice normal size**. The seminal vesicles may be affected and their enlargement can be detected on rectal palpation. Affected bulls are usually sterile when the orchitis is acute but may regain normal fertility if one testicle is undamaged. **Such bulls are potential spreaders of the disease if they are used for artificial insemination.**

- **Synovitis** *B. abortus* can often be isolated from the tissues of non-suppurative synovitis in **cattle. Hygromatous swellings**, especially of the knees, should be considered with suspicion.

- **Fistulous Withers in horses, the common association of *B.abortus*** is with chronic bursal enlargements of the **neck and withers**, or with the **navicular bursa**, causing **intermittent lameness**, and the organism has been isolated from **mares that have aborted.**
- When horses are mixed with infected cattle, some horses appear to suffer a generalized infection with clinical signs including **general stiffness, fluctuating temperature, and lethargy.**

CLINICAL PATHOLOGY:

-The major objective in the laboratory diagnosis of brucellosis is to identify animals that are infected and potentially **shedding the organism and spreading the disease.**

- Most infected animals are identifiable using the standard serologic tests, but latent infection occurs in some animals that are serologically negative. Furthermore, vaccinated animals may be serologically positive and uninfected.

-Laboratory tests used in the diagnosis of brucellosis include isolation of the organism and serologic tests for the presence of **antibodies in blood, milk**, **whey, vaginal mucus, and seminal plasma**. The organism may be present in the **cervical mucus, uterine flushings, and udder secretions** of experimentally infected cows for up to **36 days after abortion**.

- polymerase Chain Reaction (PCR):

PCR has been applied to tissues such as **aborted fetuses** and associated **maternal tissues**, **blood, nasal secretions**, **semen, and food products such as milk and soft cheeses**. *Brucella* spp. can be detected in the milk of naturally infected cattle, sheep, goats, and camels using a PCR assay that is more sensitive than the culture method.

- Serological tests:

In the absence of a positive culture of *B. abortus*, a presumptive diagnosis is usually made based on the presence of **antibodies in serum, milk, whey, vaginal mucus, or seminal plasma**. The antibody response following infection depends on whether or not the animal is pregnant and on the stage of gestation. On average, the agglutinins and complement fixation antibodies become positive **4 weeks** following experimental infection during the fourth to sixth months of gestation.

Agglutination Tests:

- Serum Agglutination Test

The serum (tube) agglutination test (SAT) or microtiter plate variants of it are some of the traditional standard tests, which are widely used.

-Rose Bengal Test (Buffered Plate Antigen or Card Test)

The rose Bengal test (RBT) is a simple, rapid spot-agglutination test using antigen stained with rose Bengal and buffered to low pH. The test detects early infection.

-Complement Fixation Test

The CFT is one of the prescribed tests for international trade and is widely accepted as a confirmatory test.

-Enzyme-Linked Immunosorbent Assays

Two main types of immunosorbent assay have been used: the **indirect and competitive formats**.

Indirect Enzyme-Linked Immunosorbent Assay **(iELISA**) has been a useful test during an eradication program, after vaccination has ceased, and for screening.

Competitive Enzyme-Linked Immunosorbent Assay:

The competitive ELISA (c-ELISA) uses monoclonal antibody specific for one of the epitopes of the *Brucella* spp., which makes it more specific than assays using cross reacting antibody. The c-ELISA is thus more specific but less sensitive than the iELISA.

-Brucellin Skin Test:

The brucellin skin test presents an alternative immunologic test that can be used to test **unvaccinated** animals. Tested animals are injected intradermally with 0.1 mL of a standardized Brucellin.

NECROPSY FINDINGS:

Lymph nodes draining the sites of the early stages of infection have marked germinal center hyperplasia and hypertrophy, accompanied by acute neutrophilic and eosinophilic **lymphadenitis.** In the later stages of the infection, lymph nodes draining mammary gland, head, and reproductive tract develop chronic granulomatous lymphadenitis

In the uterus, there is usually an **endometritis,** fibrosing mural lymphocytic **metritis,** and necrotizing vasculitis, whereas the placenta is colonized with *B. abortus* and has extensive desquamation of fetal chorioallantoic trophoblasts with subsequent hematogenous spread to villous

trophoblastic epithelium, and **necrotizing fibrinopurulent cotyledonary placentitis of the placental arcades** accompanied by granulation and intercotyledonary inflammation exudation. The placenta is usually edematous, and necrosis of the cotyledons.

In **fetuses naturally and experimentally infected** with *B. abortus*, the tissue changes include lymphoid hyperplasia in multiple lymph nodes

The affected joints usually develop a fibrinous and granulomatous synovitis with proliferative villous projection formation.

DIFFERENTIAL DIAGNOSIS:

When an abortion problem is under investigation, a systematic approach should be used. This includes a complete laboratory evaluation and follow-up inquiries into each herd. The following procedure is recommended:

• Ascertain the age of the fetus by inspection and from the breeding records.
• Take blood samples for serologic tests for **brucellosis** and **leptospirosis.**
• Examine uterine fluids and the contents of the fetal abomasum at the earliest opportunity for **trichomonads,** and subsequently by cultural methods for *B. abortus,* ***Campylobacter fetus,*** **trichomonads,** ***Listeria*** **spp., and fungi.**
• Supplement these tests by examination of urine for leptospires, and of the placenta or uterine fluid for bacteria and fungi, especially if the fetus is not available.
• Examine placenta fixed in formalin for evidence of placentitis. In the early stages of the investigation, the herd history may be of value in suggesting the possible etiologic agent. For example, in brucellosis, **abortion at 6 months** or later is the major complaint, whereas in **trichomoniasis** and **vibriosis**, failure to conceive and prolongation of the diestrual period is the usual history.

TREATMENT:

Treatment is unsuccessful because of the intracellular sequestration of the organisms in lymph nodes, the mammary gland, and reproductive organs. ***Brucella*** **spp**. are f**acultative**

intracellular bacteria that can survive and multiply within the cells of the macrophage system. Treatment failures are considered to be caused by the inability of the drug to penetrate the cell membrane barrier instead of the development of antimicrobial resistance.

CONTROL AND ERADICATION:

The major components of a control and eradication program are as follows.

- **Test and Reduction of Reservoir of Infection** All breeding cattle in the herd are tested, and those that are **positive are culled and sent for slaughter**. This removes infected cows from the herd and reduces exposure and transmission within the herd. Of particular importance is the detection and removal of infected cows before parturition.

Control by Vaccination:

Because of the serious economic and medical consequences of brucellosis, efforts have been made to prevent the infection through the use of vaccines.

Historically brucellosis vaccines were composed of attenuated strains of *B. abortus* and *B. melitensis*. Another inconvenience of these whole cell vaccines was that they interfere with diagnostic assays detecting antibody against the O-side chain of the *Brucella* LPS. Currently vaccines used to protect livestock against infection with *B. abortus* contain one of **three attenuated live strains of *B. abortus* strain 19, RB51, and strain 82**.

Vaccines containing the live *B. abortus* strain19 are the most widely used vaccines to prevent bovine brucellosis.