International Journal of Fauna and Biological Studies
Available online at www.faunajournal.com

E-ISSN 2347-2677
P-ISSN 2394-0522
www.faunajournal.com
IJFBS 2021; 8(2): 10-13
Received: 06-01-2021
Accepted: 09-02-2021

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An overview of brucellosis in cattle and human

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Abstract
Bacteria of the genus *Brucella* cause brucellosis, one of the world's neglected zoonotic diseases. The infection of the disease cause lifetime sterility in human beings. In recent time, there is an in-infection rates between and within the species. Lacking in the resources, poor management and lack of awareness are major factors in the spread of the disease. Abortion in the last trimester is a predominant sign, of the disease in cattle. Besides this, reduced milk yield and high temperature is also observed in the affected animals, while in humans it is characterized by undulant fever, general malaise, and arthritis. While the clinical picture of brucellosis in humans and cattle is not clear and often misleading. In this review, several aspects of management, diagnosis, control, treatment, and preventive aspects are reviewed.

Keywords: Brucellosis, zoonoses, malta fever, coombs test

Introduction
Brucellosis is the infection caused by the bacteria "*Brucella*". The disease is known since late Roman era. The etymology is due to its first expounded by Sir David Bruce, Hughes, and Zammit while working in Malta; hence the name 'Malta fever' is occasionally used for typical fever conditions caused by *Brucella. Brucella* are Gram-negative, non-spore-forming, non-motile, coccobacilli aerobic organism. Three species (*B. melitensis, B. abortus, B. suis*) are important human pathogens. *B. canis* is of lesser importance. *B. abortus* and *B. melitensis* are the key bovine brucellosis bacteria. Species are differentiated by production of urease and H_2S, dye sensitivity, cell wall antigens and phage sensitivity. The major species are divided into multiple biovars [1].

Brucellosis infection in the herds causes negative impacts on livestock production and reproduction performance. Compromised livestock production is due to the abortion especially during the last trimester, retention of placenta, metritis, birth of weak calves, infertility in bulls and cows and almost 20% reduction in milk production from infected cows [2]. This is how the disease causes reduced yield of milk and meat due to reduced reproductive efficiency.

Globally, brucellosis is described as a highly contagious zoonotic disease [3]. *Brucella* infection is commonly mediated by direct contact with the placenta, foetus, foetal fluids, vaginal discharges, and products (*e.g.*, milk, meat, and cheese) from infected animals. This is how the common route of infection is either direct ingestion or via mucous membranes, broken skin, and in rare cases intact skin [4]. Some repots evident that transmission of the disease is possible by in utero (vertical) transmission, person-to-person transmission, and transmission associated with tissue transplantation have been observed in rare cases [5]. There is a threat of aerial and mucosal transmission in the human beings.

Epidemiology of Brucellosis
Brucellosis has been reported in 86 countries worldwide and is a serious threat not only to livestock but also to human health globally. Endemic areas for brucellosis include countries of the Mediterranean basin, Middle East, Central Asia, China, the Indian subcontinent, sub-Saharan Africa, and parts of Mexico and Central and South America. Worldwide, approximately 5,00,000 cases are reported annually and there are an estimated 2.4 billion people at risk [6]. All age groups and both sexes are affected. Many researchers have suggested that the children and young adults are the most susceptible to the diseases while the prevalence of the disease gets lower after the age of the 60 [7]. The disease affects males and females equally [8]. The prevalence of brucellosis has been increasing due to growing international tourism and migration.

Many a time this agent is used as the potent agent for the bio-terrorism [9, 10].

Brucellosis in India was recognized early in the previous century and since then has been reported from almost all the states. The serological studies have reported prevalence rate of 5% in cattle, 3% in buffaloes, 8.23% in sheep, and 4.43% in goats. A wide variation in the prevalence of human brucellosis ranging from 0.8 to 26.6% has been reported by various researchers [7]. Brucellosis is an endemic disease in India. It is widely prevalent in all the domesticated species of animals and in humans as well. Despite having the knowledge about the disease and its easy mode of transmission, the disease has connections with the customs of the peoples [11]. Consumption of raw goat milk with herbal extracts, crushing the umbilical cord of new-born calf with teeth and consumption of undercooked meat and milk are the risk factors [12].

Occupation has the linkage in the disease transmission. Several professions like veterinary professional, inseminators, livestock inspectors, butchers and stake holders are at an increased risk of the disease.

Clinical Signs in Cattle

Brucellosis is a widespread reproductive disease affects both males and females. The organisms are mainly causing abortion, death of young ones, stillbirth, retention of the foetal membranes or birth of weak calves, delayed calving, male infertility, and marked reduction in milk yield. Almost all the domesticated animals are susceptible to the disease, except cats [13]. In bulls, the disease is characterized by fever, vesiculitis, orchitis, and epididymitis. In severe cases, it can also be the reason for testicular abscesses, metritis or orchitis that can lead to lifetime infertility. In animals, brucellosis symptoms can be varied from severe acute to sub-acute or chronic, depending upon the organ of infection and the type of animal. When a pregnant animal is infected by *Brucella*, a visible swelling of the mammary gland to the navel region and bleeding from the vagina is not uncommon, even if the cow does not abort. The enlarged udder size (appearance of the 9th month of a pregnant cow) could be used as an indication for the high stage of the disease, where animals shed bacteria in urine, milk, and vaginal discharges [14].

Clinical signs in Human

Human brucellosis is known by many different names such as Malta fever, Cyprus or Mediterranean fever, intermittent typhoid, rock fever of Gibraltar, and more commonly, undulant fever. The incubation period of the disease is almost four months and the severity of the disease is mild in children compared to the adults.

Fever is one of the most common symptoms across patients; intermittent in 60% of patients with acute and chronic brucellosis, while undulant in 40% of patients with subacute brucellosis. Fever is thought to be linked to relative bradycardia and fever of unknown origin is a more common initial diagnosis in patients in areas of low endemicity. Nearly 80% of patients suffer from chills, and 20% of patients develop a cough and dyspnoea without any active pulmonary involvement. Additionally, pleuritic chest pain may affect patients with underlying empyema [14].

Brucellosis increases the risk of spontaneous abortion, premature delivery, miscarriage, and intrauterine infection with foetal death in humans as well, which is accompanied with malaise, fatigue, and arthritis. Septicaemia with sudden onset followed by high fever, emaciation, restlessness, undulant fever, sexual impotence, insomnia, headache, loss of appetite, and weight loss can also be seen in an infected patient. The detailed symptoms of brucellosis have been documented; however, due to their protean and complex nature, clinical manifestations cannot be relied on for diagnosis. In humans, brucellosis is not confined to the reproductive system, but is also known to cause neurobrucellosis with clinical manifestation of meningitis, encephalitis, stroke, radiculitis, myelitis, peripheral neuropathies, and neuropsychiatric features. It is also evident that reported sensorineural deafness, spastic paraparesis, followed by brisk tendon reflexes, bilateral ankle clonus, and extensor plantar responses [15].

Diagnosis of the Disease

There is no gold standard test available for the diagnosis, but the conventional serological methods are useful for the diagnosis of the disease. During the first week of illness, the changes in immunoglobulin (Ig) M antibodies are predominantly present, as the time passes the IgG levels hike in the second week [16]. The titers of both subtypes continuously increase and reaches the peak within four weeks. All the diagnostic test implied for veterinary or medical diagnosis are based on antigen-antibody reaction.

Milk Ring Test (MRT)

The MRT is regarded as the herd test. It is a satisfactory and inexpensive test for the surveillance of dairy herds for brucellosis. A small sample of pooled fresh milk or cream, from no more than 25 cows, is tested and the herd is classified only as suspicious or negative. Final determination of the status of a suspicious herd and each animal in it is accomplished by blood testing. The more frequently a herd is tested with the milk ring test, the more effective the test becomes as a method to detect early infections, preventing serious outbreaks in susceptible herds. At least three tests done annually are now required by some regulatory agencies. The major limitation of the test is the dilution factor, which occurs in large dairy herds where large quantities of milk are stored in bulk tanks. To adjust for this dilution effect, larger sample volumes are used with increasing herd size. Although 1 mL of bulk milk is required for herds with up to 150 head, the use of 2 mL for herds between 150 and 450 head and 3 mL for herds with 450 to 700 head has been advised [17].

Standard Tube Agglutination Test (STAT / SAT)

STAT has been used extensively for many years in the diagnosis and surveillance of brucellosis. STAT is performed by mixing whole bacterial cell antigens with serum and incubating the mixture. Since the test is performed at neutral pH, it primarily detects IgM isotype. Even though STAT is sensitive, as it detects IgG less efficiently, the test is considered less specific. Though simpler and cheaper to perform, the test lacks specificity which enables it to be used as a supplementary test in the absence of alternative methods. However, addition of EDTA (5 mM final test dilution) to the antigen reduces the chance of cross-reactions and hence, the test is reported to improve specificity markedly. TAT is generally used in combination with other tests rather than as a single detection method. In human beings, a STAT titre in excess of 1:160 coupled with clinical presentation is considered to be a presumptive case while, in endemic areas,

titres of more than 1:320 are regarded as more specific [18].

Rose Bengal Plate Test

RBPT is a simple spot agglutination test using the Rose Bengal stained antigen and buffered to acidic pH. RBPT is based on the ability of IgM antibodies present in the sera to bind to the coloured antigen at low pH. The test is an excellent screening assay, but may be oversensitive for diagnosis in individual animals, especially vaccinated ones. Though RBPT is very sensitive, like other assays, it could give an occasional positive result in cattle because of *B. abortus* S19 vaccination or for false-positive sero reactions (FPSR). Likewise, small ruminants and pigs affected by FPSR or vaccinated with *B. melitensis* Rev1 exhibit the same phenomenon. So, the positive reactions should be further investigated using suitable confirmatory strategies like epidemiological investigations. In contrary, false negatives occur rarely. However, RBPT remains as an adequate assay for detecting infected herds and it guarantees the absence of infection in brucellosis-free herds.

Coombs Test

Coombs test, also known as anti-globulin test, detects the antibodies that may agglutinate to the red blood cells and cause haemolysis [15]. Normally, no direct agglutination takes place with red cells coated with IgG or complement and red cells are said to be sensitized with complement or IgG. For an agglutination to occur, an additional antibody that reacts with the Fc portion of the IgG or with the C3b or C3d component of the complement must be added to the system forming a bridge between the antibodies or complement coated red cells resulting in agglutination [18]. A direct Coombs test is observed when antibodies are located on the red cells and haemolysis is mediated through the host immune system IgG-ELISA and Coombs test are reported to have good correlation; nonetheless, the ELISA and Coombs test remain positive more than other agglutination assays. Coombs test titre will remain high with chronic long-term Brucella infection, even before the diagnosis is made. In acute brucellosis, the Coombs titre remains 4–16 times higher than the STAT titres; whereas, the titres are 16–256 times higher in chronic patients without treatment [15].

Enzyme Linked Immunosorbent Assay

Enzyme-linked immunosorbent assay (ELISA) is the most efficient test for serodiagnosis of brucellosis because of its high sensitivity and specificity. This test has been widely used to identify and quantify different kinds of anti-Brucella immunoglobulins (IgM, IgG and IgA). Overall, it has been stated that ELISA has a sensitivity of 83.3% for IgM based Brucella antibodies and 41.7% for IgG Brucella antibodies, while the combined specificity for both i.e., IgM and IgG was 92.3%. The sensitivity of iELISA varies between 96% and 100% and specificity from 93.8% to 100%. ELISA is an excellent test for screening large populations and aids in the differentiation of acute and chronic forms of the disease. Further, it is a test of choice, especially when other tests are negative and the case under investigation is clinically suspicious [18].

Treatment

There is no treatment for Brucellosis in animals. It is controlled by official vaccination and entire herd testing with slaughter of reactors. Quarantines are imposed by state and federal authorities until the herd is proven free of disease. Animals are also blood tested at slaughter and positive reactors traced back to the farm of origin. Vaccines have used different strains of brucella for creation, such as RB-51, so animals vaccinated can be differentiated from naturally infected animal.

In uncomplicated brucellosis in adult patients, doxycycline-aminoglycoside combination is the first choice with doxycycline- rifampin and doxycycline-cotrimoxazole should be the alternative regimens. The other oral regimens including quinolones may be considered as alternatives. Cotrimoxazole plus rifampin for six weeks may be the regimen of choice for the treatment of patients younger than 8 years old. Gentamicin for 5 days plus cotrimoxazole for six weeks may be a suitable alternative regimen [19].

Prevention and Control

The most rational approach for preventing human brucellosis is the control and elimination of the infection in animals. Pasteurization of milk is another protective mechanism. Vaccination of cattle is recommended for control of bovine brucellosis in enzootic areas with high prevalence rates. The same holds true for goat and sheep brucellosis. Eradication by testing and culling is the way to the elimination of brucellosis in regions with a low prevalence [20].

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