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Brucellosis as a human threatening and economic disease

Hibbat Al Rahman .R.Ricad

Al Kunooze university college, Basrah,, Iraq

mailto:hibat9408@gmail.com

Abstract

This review study aimed to collect information about Brucellosis as a disease that has an impact on humans from several aspects, whether from the health or economic aspect.

Brucellosis is one of the most common contagious and communicable zoonotic diseases with high rates of morbidity and lifetime sterility, caused by genus *Brucella*.

Brucella is a Gram-negative, aerobic, and facultative intracellular coccobacillus, and due to its complex nature, brucellosis remains a serious threat to public health and livestock in developing countries.

There are various diagnostic tests employed for the diagnosis of brucellosis including culture, serological, immunopathological and molecular methods, but the quantitative or real-time polymerase chain reaction (qPCR) assay is specific and highly sensitive and could be an appropriate method for the rapid and safe detection of the genus *Brucella*.

Keywords

Brucellosis, *Brucella*, Pathogenicity, Diagnosis.

1. Introduction

Brucellosis is a highly infectious zoonotic disease and an economically important infection of humans and livestock with a worldwide distribution. It is a major veterinary and human public health problem in most parts of the world. The incidence of this disease is greatly decreased in the developed world due to effective vaccination based control programs, but remains an uncontrolled problem in regions of high endemicity such as the Mediterranean, Middle East, Africa, Latin America and parts of Asia including India [1-3].

Brucellosis is caused by *Brucella*, a Gram-negative, aerobic, and facultative intracellular coccobacillus [4]. Based on taxonomic distribution, *Brucella* is classified as α-proteobacteria, which is further divided into six species, each including several boars. The species *B. melitensis* boars 1–3 have been reported in sheep and goats, and *B. abort us* boars 1–6 and 9 in cattle. Similarly, the *B. suis* biovars 1–3 are known to infect pigs, while *B. suis* biovar 4 and 5 are more common for infection in reindeer and small rodents. Among other common species, *B. canis* is found in dogs, *B. ovis* in sheep, and *B. neotomae* in desert wood rats. Recently, *B. pinnipedialis* (in seals) and *B. ceti* (in whales and dolphins) are newly reported species, infecting marine animals [5].

Five out of the nine known *Brucella* species can infect humans and the most pathogenic and invasive species for human is *B. melitensis*, followed in descending order by *B. suis*, *B. abortus* and *B. canis* [6]. The zoonotic nature of the marine *Brucella* (*B. ceti*) has been documented, *B. melitensis*, *B. suis and B. abortus* are listed as potential bio-weapons by the Centers for Disease Control and Prevention in the USA. This is due to the highly infectious nature of all three species, as they can be readily aerosolized. Moreover, an outbreak of brucellosis would be difficult to detect because the initial symptoms are easily confused with those of influenza [7].

Human brucellosis is at the origin of many symptoms namely undulating fever, malaise, fatigue, and anorexia. If untreated, it may progress into a chronic phase, characterized by the appearance of severe complications like endocarditis, orchitis, spondylitis, osteomyelitis, arthritis, meningoencephalitis, and recurring febrile conditions [8]. In domestic animals, such as cattle, sheep, goats, and swine, major consequences include abortion and metritis in females, and orchiepididymitis and infertility in males [9], resulting in reduced fertility and a significant decline in milk production [10].

2. History of brucellosis:

Marston made the earliest recorded description of brucellosis in 1859 as he wrote of an illness, including his own, which differed from typhoid fever. Sir David Bruce isolated the organism from the spleen of a patient while investigating an outbreak of a fatal disease known as Mediterranean or Malta fever, affecting British soldiers stationed on the island of Malta [11]. He named the bacteria as Micrococcus melitensis due to coccidian morphology. Hughes suggested the name undulant fever (wave like) because of characteristic fever, which rise and fall over weeks in untreated patients [12]. Write and Smith detected antibodies of M. melitensis through agglutination test in humans and explained the zoonotic potential of this disease [13] Summit working with Mediterranean fever commission discovered the role of goats in brucellosis by isolation the organism from the milk and urine of the goats and concluded that goat was the reservoir and declared that consumption of the raw milk and cheese responsible for the human brucellosis [14]. The report of isolation of a gram-negative rod from cattle, its subsequent establishment of similarity between M. melitensis gave convincing evidence that both organisms could not be differentiated morphologically or by cultural and biochemical reactions. Both these bacteria were finally placed under one genus Brucella named in honour of Sir David Bruce.

3. Transmission of Brucellosis:

There are three main transmission ways. People can be infected through eating undercooked meat and unpasteurized dairy products both which are carrying *Brucella*. Meanwhile, people get infected by inhaling *Brucella*, mainly laboratory workers who work with the bacteria. In addition, can also infect workers who are in close contact with animals or animal waste can be infected by the skin, wounds or mucous membranes, containing slaughterhouse workers, meat-packing plant employees, veterinarians and even hunters. Although there are a small number of reports of vertical and horizontal transmission between humans [15], it is generally acknowledged that human-to–human transmission of the infection is a very rare event [16].

3. Infection:

Brucella organisms enter into their host through the mucosal membranes of the respiratory and digestive tracts [17]. Once inside, local professional phagocytes such as macrophages, dendritic cells, and neutrophils internalize the bacteria and move to the closest draining lymph nodes following the normal sampling of the immune

system. This leads to subsequent dissemination to the different organs of the reticuloendothelial system, including lungs, spleen, liver, and bone marrow [18]. In pregnant animals, *Brucella* displays a strong tropism for placental trophoblasts [19–21] and for mammary glands [22], in which it replicates extensively causing placentas and abortion in the last trimester of pregnancy in ruminants [23]. In humans, brucellosis is a systemic infection and any organ can become infected, albeit with some predilection for joints and liver and at lower levels for the brain and heart [24].

5. Pathogenicity and Virulence:

Brucella spp. are facultative intracellular organisms, surviving and multiplying within cells of reticuloendothelial system (RES) and their disease spectrum is partially explained by the ability of the organism to evade host defines mechanisms by virtue of intracellular existence. Survival and multiplication of *Brucella* organisms in phagocytic cells are features essential to establishment, development, and chronicity of the disease (25). Soon after entry into the body, polymorph nuclear and mononuclear phagocytes ingest the bacteria. After ingestion by phagocytes, the organisms proliferate in the local lymph nodes. The infection spreads hematogeneously to tissues rich in elements of RES, including the liver, bone marrow, lymph nodes and spleen. Organisms may also localize in other tissues, including joints, the central nervous system, the heart and the kidneys (26). Bracelet form granulomas made up of epithelia cells, polymorph nuclear leukocytes, lymphocytes, and giant cells in tissues and organs. Granulomas are known to be more frequent in B. aborts infections. Although toxaemia is commonly observed in B. melitensis, abscess formation in joints and spleen is more often related to B. sues (27). Multiplication continues within macrophages and monocytes, and eventually the cells are killed, releasing the organisms. The “undulant” waxing-and-waning fever pattern seen in brucellosis is associated with the periodic release of bacteria and their components from phagocytic cells. Release of bacteria into the peripheral circulation results in haematogenous seeding of other organs and tissues, thereby leading to the protean clinical manifestations of human brucellosis. Relapses and recurrences of illness are kept in check to some degree by a balance between the virulence of the organism and the presence of an intact, functional cellular immune response. As with other intracellular pathogens, humeral antibodies are produced, but cellular immune defense mechanisms are required to kill the bacteria (28). The clinical spectrum of brucellosis depends on many factors, including the immune status of the host, the presence of other underlying diseases or conditions, and the species of infecting organisms. The greater virulence of B. melitensis and B. suis has been supported by in vivo studies with experimentally infected animals and by in vitro work examining phagocytosis, intracellular survival, and lymphocyte responses to the different species. Disease

caused by B. aborts and B. canes are insidious in their onset, but tend to cause milder constitutional symptoms and less severe complications (28). Cellular immunity has a fundamental role in controlling the disease. Although the presence of specific antibodies is of utmost importance in diagnosis, they play a limited role in the immune response. The IgM antibodies increase in the first week and the IgG antibodies in the second. After 4 weeks of rising both Ig levels decrease rapidly through a successful treatment. Furthermore, IgG levels decrease faster than IgM levels with treatment. Even after eradication of active infection, IgM antibodies can remain positive in low titres for months or even years. A high level of IgG and IgA antibodies for longer than 6 months is a sign of chronic infection or relapse (27)

6. Human Brucellosis:

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 [29]. The usual incubation period of one to four weeks can be extended up to several months before complete symptoms appear. Infection among children is generally more benign than in adults, concerning the likelihood and severity of complications and response to treatment [30].

Fever is one of the most common symptoms across patients [31]. The acute fever in humans is frequently associated with bacteraemia as *Bracelet* spread from the lymph nodes that drain the site of incursion and distribute throughout the reticuloendothelial system. This usually occurs within 1 to 6 weeks of exposure but may vary according to the individual, the route of entry, the virulence of the infecting strain and the magnitude of the infectious dose. The maximum temperature of the fever is usually within 38-41C but May sometimes be substantially higher leading to hyperpyrexia and occasionally death. Typically the temperature is near normal during the early part of the day and then rises sharply. After reaching a peak the temperature falls rapidly accompanied by profuse sweating. This process gives rise to the term ‘undulant fever’ and is most frequently observed in untreated cases where the disease has persisted for some time [32]. Common symptoms also include malaise, insomnia, anorexia, headache, arthralgia, constipation, sexual impotence, nervousness and depression, Human brucellosis is also known for complications and involvement of internal organs and its symptoms can be very diverse depending on the site of infection and include encephalitis, meningitis, spondylitis, arthritis, endocarditis, orchitis, and prostatitis (33). Spontaneous abortions, mostly in the first and second trimesters of pregnancy, are seen in pregnant women infected with Brucella (34).

7- Diagnosis

There are various ancillary tests employed for the diagnosis of brucellosis including culture, serological, immunopathological and molecular methods. Of these, culture method has high specificity but is time consuming and requires laboratory facilities with an appropriate degree of biosafety [35], also poor sensitivity, the low sensitivity for isolation is dependent on many factors including; the individual laboratory practices, quantity of pathogen in clinical samples, stage of infection, use of antibiotics before diagnoses, the methods used for culturing and the cultured strain (*B. melitensis* is more readily cultured from clinical sample than *B. aborts*). The sensitivity of detection varies from 15% to 70% of acutely infected patients and is even lower in chronically infected patients. Recently, higher rates of positive blood cultures (91% in acute brucellosis and 74% in chronic brucellosis) have been reported by lists centrifugation technique [36].

Various serological tests are employed for diagnosis with varying degree of sensitivity and specificity. However, cross-reactions between *Brucella* species and other Gram-negative bacteria are a major problem of the serological assays [37]. Furthermore, serology tests do not reveal which *Brucella spp*. is causing infection in the host, and this precludes the possibility of identifying the infection source, which is important to know when planning and implementing appropriate control measures [38].

Genetic characterization using molecular DNA technology allows molecular typing of *Brucella* without having to handle living *Brucella* organisms [39]. The quantitative or real-time polymerase chain reaction (qPCR) assay targeting the insertion element IS711 is specific and highly sensitive and could be an appropriate method for the rapid and safe detection of the genus *Brucella* [40]. Further classification of *Brucella* at the species level can be performed by qPCR targeting the *rpoB* gene [41]

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