



## A Study of Brucella Infection in Humans

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### Abstract

**Objective:** Brucellosis is the most usual zoonotic disease around the world especially in the Middle East, Mediterranean and Indian sub-continent areas. This bacterium has ten species that *Brucella melitensis* among them recognized as the most important cause of human brucellosis. This infection transfer ways to human include of wounds, bacteria inhalation and consumption of septic dairy such as raw milk, cream and butter. Brucellosis as a systemic disease can involve more organs of patients that have symptoms such as fever, night sweating, and backache. This infection can be divided as acute, sub-acute and chronic forms according to the manner of clinical presentation.

**Materials and Methods:** This research is a review study and conducted by reviewing of the literature, which is related to this issue and also visiting, PubMed, and other linked websites.

**Results:** In human brucellosis domestic animals are the main natural reservoir of infection. Whenever incidence rate of this infection in domestic and wild animals is reduced on the other hand incidence rate in human also will reduce.

**Conclusion:** Blood cultures, serological tests and molecular tests are common laboratory methods of this infection. Diminution of relapse and therapeutic failure rates are as most important aim, which is researcher's regards.

**Keywords:** Diagnostic test, Human Brucellosis, Therapeutic Regimen, Zoonotic

### Introduction

Brucellosis is an infectious zoonotic disease which caused by bacteria of the genus *Brucella* that has wide spreads in the world. Brucellosis is an ancient condition disease, conclusion of the recent study of the old age Egyptian skeleton related to around 750 BC, sacroiliitis and common complexities of brucellosis were documented (1). The disease was defined in the bones of corps of 250 people who died in 79 AD (2). David Bruce, a British army surgeon, in 1886 detached a coccobacillus from the spleen of a man who had died of «malta fever» disease. Then he called it «*Micrococcus melitensis*» (3). In 1897, Bang found *Brucella abortus* as the main cause of abortion in Cow. In 1914 traum isolated *Brucella suis* from Pig. In 1956 Buddle and Boyce also discovered

*Brucella ovis*. In 1957 Stonner and Lackman detached *Brucella neotomae* from Rat. In 1968 Carmicheal and Bruner isolated *Brucella canis* from Dog. In 1990s *Brucella pinnipediae*, *Brucella cetaceae* and *Brucella delphini* discovered from marine mammals and explorer called this strain experimental name as *Brucella maris* (4-7). *B. melitensis*, *B. abortus*, *B. suis* and *Brucella canis* can be caused *Brucella* infection in human. Moreover, the first three species are the most cause of infection in both human and animal (8). *Brucella* species referred to marine mammals have been showed as another reason in human infection (9). Due to low dose of transferable infectious, makes possible this bacterium as biological weapon (10). *Brucella* consists of coccobacilli Gram-negative, intracellular,

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aerobic and motionless. Meanwhile the bacterium is non-capsulated (11).

These bacteria are oxidase, catalase, urease and nitrate reductase positive. *Brucella* bacteria is of 0.5-0.7  $\mu$  in diameter and 0.6-1.5  $\mu$  in length (5). *Brucella* species are part of normal flora of the genitourinary of cow, sheep, goat, and dog (8). Organism belongs to subdivision of  $\alpha$ -2 from Proteobacteria accompany with *Ochrobactrum*, *Rhodobacter*, *Rhizobium*, *Agrobacterium*, *Bartonella* and *Rickettsia* (12).

### Genome

*Brucella* genome includes of two circular chromosomes, in which chromosome I, is 2.1 Mb and chromosome II is 1.18 Mb (13,14). *B. melitensis* consists of two circular Replicons and size of these Replicons are approximately 1.1 Mb and 2.2 Mb. *B. abortus* biovar 1,4 and *B. suis* biotype 1 are similar to *B. melitensis*. While *B. suis* biotype 3 is consisted of a uni chromosome of 3.3 Mb (15).

### Antigenic components

Lipopolysaccharide (LPS) specially induces powerful antigenic responses (16). Smooth LPS (S-LPS) consists of two types: A and M. A antigen is major in *B. abortus* and *B. suis*, whereas M antigen is major in *B. melitensis*. Non-smooth LPS (R-LPS) is as similar as S-LPS that is a Bacteria's antigen. O-chain has been reported as a reason of cross-reaction in Agglutination test and complement fixation test (CFT) between species of Smooth brucella, *Yersinia enterocolitica* 0:9, *Escherichia coli* 0:157, *Salmonella* 0:30, *Vibrio cholerae* and *Stenotrophomonas maltophilia* 0:1 (17). Some kinds of protein antigens such as cytoplasmic, periplasmic and outer membrane structural protein like Omp 25 can be also detected by the immune system of the host in *Brucella* infection (18). Omp 25 porin is considered as a negative regulator of tumor necrosis factor (TNF $\alpha$ ) production (19). Recent research has indicated the lipoprotein (Omp 19) which is considered as a negative regulator of interferon gamma (IFN $\gamma$ ) (20).

### Pathogenicity

Some elements such as LPS, 24 KD protein, urease enzyme, VirB have the necessary role in pathogenicity of brucellosis. LPS is relatively deficient motivator of IFN $\gamma$  and TNF $\alpha$ , both of which are necessary for the elimination of the microorganism (21,22). Survival in macrophage is depended on the construction of stress inducer protein like 24 KD, which is an inducer of the acid environment (23). Urease enzyme has a protective role of microorganisms in the stomach, when they inter orally to the host body. H<sub>2</sub> receptor blockers increase possibility of Brucellosis infections (24).

*Brucella* induces VirB operon in stress environment like nutritional deprivation, while VirB operon is encoding Type IV secretion system (T4SS) as a membrane-associated transporter. More over T4SS has an important role in extended of *Brucella*

containing vacuoles (BCV) in host body, BCV is limited to the extent of fusion to lysosome (25).

*Brucella* can be suffering host body in some ways, such as: breathing, swallowing, contact between in juried skin and slinked fetus (26,27). After entry of bacteria to the human body, they are being taken by local Lymphocyte, which by Lymph nodes and circulation come to different body organs, of course with more tendency come to the reticuloendothelial system.

The cell-mediated immunity, macrophages and dendritic cell have the imperative role against *Brucella* infections (28).

It should be mentioned that humoral immune system expands in brucellosis patients.

### Epidemiology

Human brucellosis is one of the most usual zoonotic disease with more than annually 500/000 new cases around the world (2). This infection is endemic in south and center of America, Africa, Indian subcontinent, Middle East and Mediterranean countries (29). Incidence has been reported in an endemic area from 1.1 > to 200< per 100/000 population (30). Maybe reported incidence in an endemic area is low, for low level of reports and wrong diagnosis (31). Rate of annual incidence is as per million populations in some countries, this rate is in the top level. These countries consist of Saudi Arabia, Iran, Turkey and in addition maximum of incidence had been reported in Syria (32). However, it's necessary to mention that the real incidence of human Brucellosis is unknown (24). According to World Health Organization (WHO) real incidence is almost 10 times more than some deal that had been reported (33). *B. melitensis* is one of Brucellosis disease that human is affected there (15). Re-emerge of this disease in Malta and Oman indicates onerous extirpation of this infection (34). Sheep and goat and their productions are the most important source of *B. melitensis* infection in human, although the *B. melitensis* in cattle has been emerged as a major problem in some southern European countries and also in Saudi Arabia and Kuwait.

Processing milk, hygienic environment, and climate condition are the most significant factors on transmission of this infection. Contact with infected domestic animal is often one of the transmission manners of Brucellosis infection to human, although some cases of transmission from human to human of this disease has been reported too (35,36). Sexual transmission of this infection is so rare, but this kind of transmissibility is still controversial (37). Persons who are living in endemic areas and suffering from HIV infection, liver disease and chronic renal disease have equivalent risk of Brucellosis infection as a healthy person (38). Consumption of unpasteurized raw milk, soft cheese, ice cream, butter is the most usual transmission way. Hard cheese, yogurt for lactic fermentation have a lower risk than the first category (15). Usage of rare spleen and liver can also

make human infected. Laboratory staff can become infected accidentally on the job with cultivation environment the strain, virulent via touching or bacteria inhalation. In addition, vets, farmers, shepherds, and abattoirs staffs are persons who are in high risk (39). Brucellosis is generally rural disease, because farmers in this region have contact with their animals and use of their unpasteurized dairy products, although sales of these products makes transmission so possible to urban areas.

### **Human disease**

Brucellosis is a systemic disease which can suffer each organ of the body. Incubation period of this infection are between 1 and 3 weeks, but can take several months before demonstrations of disease signs. The most common nonspecific symptoms of brucellosis consist of fever, it be seen alternatively in 60% of patients both in acute and chronic types. And undulant fever with the same rate in sub-acute patients is observable (2). Moreover a night sweats, asthenia, insomnia, anorexia and headache are also observable (40). According to duration and intensity of symptoms, this disease can be divided as: acute period (lower than 2 months), sub-acute (2months to 1 year), chronic (more than 1 year).

#### **Acute form**

In this form of the disease, most of the patients have the same symptoms including fever, headache, backache, losing weight and anorexia, infection in this form is also the same as febrile influenza. It should be mentioned that the splenomegaly and hepatomegaly in 50-60% of cases are observable (41,42).

#### **Sub-acute form**

In this category are patients who do not receive sufficient antibiotic treatment, so relapse their disease. And patients who don't receive proper antibiotic because of wrong diagnosis (40).

#### **Chronic form**

This form is intermittently observable in the old person, patients in this form have fever so rarely, and there is a local infection like Uveitis in some cases (40).

Brucellosis mostly engages internal organs and relates to an infection position, their symptoms are different. For example Spondylitis is one of the most serious side-effects of brucellosis and targets especially lumbar vertebrae of old patients (43). Meningitis, encephalitis, and brain abscesses are also the most important other involvements of central nervous system in brucellosis (44). Endocarditis is expressed as the cause of at least 80% of mortality due to brucellosis, in which aortic valve and mitral valve are generally infected (45). An arthritis and genitourinary systems involvement like orchitis are also observable in brucellosis. It's necessary to mentioned that mild leukopenia, lymphocytosis mid, mild anemia and thrombocytopenia are also observable in this infection (15). Symptom of brucellosis is usually fever mid unfamiliar origin and hence it can be confused with some diseases such as;

malaria, tuberculosis, cholecystitis, fungal infection, autoimmune diseases, and tumors (5).

### **Diagnosis**

For detecting patients who are suffered from brucellosis, past medical history should be evaluated, and routine Hematology, biochemical tests and Echocardiography, Brucella culture, serological and molecular tests should also be done. Routine laboratory tests are not usually so helpful in brucellosis detection (46). For example: white blood cell counts in these patients are in normal or low level. A deterministic way of brucellosis diagnosis is confirmed the presence of Microorganism via blood cultures, or cultures of bone marrow's (BM) patient. It's necessary to mentioned that the BM cultures presented as Gold standard in some studies (47). In the acute form of brucellosis, sensitivity of blood cultures has been reported more than 80%. However in the chronic form, sensitivity has been recommended 30%-70% (48). One of the problems of this method is slow growth of Brucella bacteria, while in biphasic Ruiz-Castaneda method, the incubation period is almost long for 6 weeks (47). Although in a new system of blood cultures, sufficient time for organism diagnosis is lower. For example; in Becton Dickinson Diagnostic system, Sparks, MD, USA (BACTEC™) culture system, diagnostic time has been reported almost 4 days (49).

Serological tests consist of:

Rose Bengal agglutination test (RB), serum agglutination test (SAT), coombs test, lateral flow assay.

RB test is very fast, easy and cheap. It can be done < 10 min and it is so helpful and useful for diagnosis of an acute form, but this test has many false-negative answers in the chronic form of infection (50).

In human brucellosis, SAT is the most common admissible serological diagnostic test (51). SAT test estimates total the amount of IgG, IgM, IgA relates to brucella. Titer above 1:160 accompany with clinical demonstration is recognizable. Further, use of SAT titer  $\geq$  1:320 and Titer 2-mercoproetanol (2 ME)  $\geq$  1:160 are more specialist, in an endemic region. It should be mentioned that the 2-mercoproetanol determines amount of dedicated IgG and neutralizes Agglutination ability of IgM. SAT in chronic patients maybe has false-negative and maybe shows in first phase Titer  $\leq$  1:160 (48). Its necessary to illustrate decisive treatment of brucellosis patients have correlations to declining SAT titers (52). Coombs test uses for diagnosis of incomplete IgG antibody (53). High sensitivity of this test for verification of relapses is noticeable.

Lateral flow assay which use for confirmation of brucellosis in affected patients in endemic areas, especially in some cases which their Rose Bengal test had been reported positive (54). Accomplishment of this test is so easy, and interpretation of that is also fast and has high sensitivity (55). Molecular tests like polymerase chain reaction (PCR) have spread for Brucella diagnosis in some decades before. PCR test

is very fast, so it can show positive results just lower than 10 days after entry of bacteria. Nowadays, PCR uses for evaluation of treatment efficacy mostly (56). In addition, real time-PCR is faster than ordinary PCR, the first one is less prone to infection and is more useful for clinical purposes (57). It must be mentioned that molecular methods like PCR in several laboratories has a different sensitivity that this point emphasis on the necessity of standardization in tests for acceptable results to use as routine tests (8). Based on something mention before diagnosis of this infection moreover accomplishment of laboratory tests such as SAT, 2 ME, Coombs, which are antibody evaluator in different stages of disease, some clinical findings like, fever, prepheral arthritis and sacroiliitis most be evaluate.

### Treatment

In human brucellosis treatment, choice of antibiotic, which can penetrate into the macrophage and can be active in an acidic environment is so important. WHO in 1986, for acute brucellosis treatment in adults offered therapeutic regimen including: Doxycycline 100 mg plus rifampin 600-900 mg for 6 weeks, and also the relapse rate had been reported about 24% (58).

The therapeutic regimen which was mentioned included of streptomycin and doxycycline which via WHO had been introduced as optimal regimen, but other studies showed that Streptomycin with doxycycline are more effective than other regimen, as the relapse rate was reported about 8% (59,60). Relapse and therapeutic failure are two important issues in treatment. As relapse which is recurrence of clinical symptoms along with bacteremia recurrence or even without that after absolute treatment, it can be occur by every kinds of therapeutic regimen. Most of the relapses take place after 6 months of treatment cessation. Therapeutic failure can also take place because of some drugs side-effects in which are along with disease symptoms return and bacteremia existence (58). Because of these two points which mentioned before, especially relapse serologically and clinically following recommended for up to two years after treatment. Trimethoprim-sulfamethoxazole (TMP-SMX) in triple therapeutic regimen in most areas is useful. In some ways TMP-SMX (800, 160 mg) with rifampin or doxycycline that recommend by some experts in two times a day which has 10% relapse (59,61). Some experts presented combination of edible doxycycline 100 mg twice a day, for 45 days with intramuscular usage of gentamicin 5 mg/kg daily for 7 days have the same reliability as usage of doxycycline for 45 days with streptomycin 1 g intramuscular daily for 14 days (58).

For neurobrucellosis patients offered combination treatment with usage of 2 or 3 medicines like streptomycin, doxycycline, rifampin and TMP-SMX (62-64). Rifampin is the main medicine in the brucellosis treatment in pregnancy period (2). Meanwhile, combination of doxycycline and co-trimoxazole in children have been also using.

Usage of doxycycline in pregnant women is prohibited because it may prevent embryo bones growth (65). In children under age of 8 who are infected by brucellosis offered combination of TMP-SMX and rifampin for 45 days (66). However for children who are over the age of 8 offered combination of doxycycline and gentamicin (67). Usage of medicine whit high immunomodulating effect like levamisole with some effects such as immunoregulator cells reduction function and increase number of lymphocytes in circulation accompany with usual antibiotic region had been reported effective in person who affected by brucellosis (68).

### Conclusion

Blood cultures, serological tests and molecular tests are 3 common laboratory diagnostic methods of this disease. In the treatment process of this infection uses different kinds of antibiotic. Streptomycin, doxycycline, rifampin are the most usual therapeutic regimen for this infection. Diminution of relapse and therapeutic failure rates are as most important aim which is researcher's regards.

### Ethical issues

The study has been approved by the local ethics committee.

### Conflict of interests

We declare that we have no conflict of interests.

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