Brucellosis in Iran: A Literature Review

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Abstract: Brucellosis is one of most important pervasive diseases common between human and livestockand is yet considered important issue in many countries around the world. Although WHO achieved successful results to control and eradicate this infectious disease in some countries, this disease is yet accounted as an important infectious disease in some, especially developing, countries. Brucellosis causes to decrease efficiency, abortion, weakness and also results in economic losses in this part of the business. This disease is transmitted directly and indirectly from infected livestock to the human, its spectrum of clinical protests is different among patients, involves many organs and the need for long-term treatment is one of the other problems beside this zoonotic disease. Iran is among countries involved with endemic brucellosis and has yet been no longer successful to eradicate this infectious bacterial agent because of its variety of resources and reservoirs and is yet taken into consideration as one important infectious disease in health field and livestock industries. [Mehrdad Assadi, Abolghasem Siyadatpanah, Katayoun Bahman Soufiani, Hayedeh Mobayyen, Khosrow Sadighbayan, Jafar Asadi, Amir EmamiZeydi, Behzad Javadian. **Brucellosis in Iran: A Literature Review**. *J Am Sci* 2013;9(3):203-208] (ISSN:1545-1003). http://www.americanscience.org. 27

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1. Introduction

Brucellosis, an infectious disease transmittable to human and livestock, is called Malta fever, Mediterranean fever, Gibraltar fever, thousand-face disease, raging fever, melitococ-cis disease in humans and contagious abortion in livestock, Bangs' disease in cattle [1].

Malta fever disease is universal in human but its aerial prevalence is dependent on infection spread and density between livestock, the contacts between human and animals or their secretions, consumption of milk and other unpasteurized dairy products [2].

Human might be infected by *B.abortu*,*B.canis*, *B. suis* and *B. melitensis*. Infection intensity Brucella types such that *B. abortu* and *B. canis* cause to mild disease while in brucellosis caused by *B. suis*, the duration is longer and symptoms are more severe.*B. melitensis* is the most abundant and acute type followed by different disturbances. Considering that Malta fever, directly or indirectly, is dependent on livestock in the area, therefore, people like ranchers, slaughterhouse workers and veterinarians are among high risk group infected by the disease [3 and 4].

2. History

In 1887, a British physician, called Bruce, separated a body mass from a soldier spleen while he had been died of a disease with symptoms like raging fever and named it *Micrococusmelitensis*. After 10 years, a Danish veterinarian Bang separated a similar mass from an aborted bovine fetal and renamed it *Bacillus abortus*. Then, another bacterium was separated by Traun from an aborted swine in 1914 and finally Evans in 1918 noticed that there is complete similarity between human, swine and bovine microbes had been separated so far. He demonstrated that the disease in human might also be made by microbes separated from livestock and proposed general name *"Brucella"* for this class of bacteria [5]. There has endemically been for many years in Iran and for the

first time in 1933, specialists in Pasteur Institute of Iran separated *Brucellamelitensis* from a human culture infected with Malta fever. From the year onward, considerable progresses achieved in construction of different Brucellosis vaccines and antigens for livestock [6].

3. Physiology and Brucella structure

Brucellas are little, non-motile, without spore, negative grambacilluses or cocobacilluses incapable with fermenting carbohydrates, variable in size, 0.6-2µ in length and 0.3-0.5µ in width. These micro-organisms are observed in groups, sometimes individually and make a chain or short strip in laboratory cultures. They are no longer resistant against acids but they can resist in decolorization by weak acids such as 5% acetic acid. This property is applied in Brucella colorization technique to identify the bacteria [7].

Brucella has no diagnostic exotoxin and endotoxin produced by Brucella has no much toxicity. The most important pathogenicity tools of this bacterium are catalase and superoxide dismutase production, prevention of phagolysosome integration and granule formation in involved organs [8].

Brucella bacterium is classified in 6 types including *B. suis, B. abortus, B. nelitensis, B. neotomae, B. canis and B. aovis* [9].

Infection agent is transmitted to the subject via consumption of foods contaminated with the bacteria, direct contact with the microorganism or inhalation of infectious particulates suspended in the air [10]. More than 500000 new infected subjects are annularly diagnosed with the disease all over the world [11].

Brucellosis in Iran

In Iran, Malta fever is considered an endemic disease reported in most provinces with more than 34 people approximately annularly infected with the disease among 100000 people [12]. It is estimated that Brucellosis prevalence is average 0.5 to 10.9 people in 100000 people in different provinces of the country [13]. Note that Malta fever is dependent on livestock, directly or indirectly, in the area. Therefore, people like ranchers, slaughterhouse workers and veterinarians are in high risk group infected with the disease [14].

Although, many programs have implemented to eradicate and control Malta fever in most involved countries, most efforts have been approximately done to remove this disease and its microbial reservoirs from involved livestock. This is usually conducted by livestock vaccination, an experience which resulted in totally disease eradication in some countries such as Portugal [15]. Studies conducted in some countries including Italia, Mexico and Saudi Arabia about livestock vaccination effects against Brucellosis, followed by distribution procedure in these countries, indicate severe decline and descending procedure of the disease involvement in human beings [16 and 17].

In Iran, Brucellosis vaccine production and livestock vaccination against the disease was initiated in 1963. According to the researches in livestock, prevalence rate has been declined in recent years from 45% in 1.8% [18]. In a study conducted in some cities in Mazandaran Province in 1999, prevalence rate of 20%-50% was reported in citizens [19] but in a similar study conducted in mentioned province in 2012, prevalence rate was estimated 0.7%-24% among the people [20].

The rate is different in the world countries such that in a map drawn based on Brucellosis dispersion in 2006, in some countries like Northern America, Canada and Australia, the disease in very rare and less than 2 in 100000 people while in Syria and Mongolia, prevalence rate is more than 500 in 100000 people. Also, prevalence rate in Iran is 50-500 in 100000 people [21]. Rahnema et al. in their 2001-2005 study evaluated the disease prevalence rate in Golestan Province as 29, 33, 67, 24 and 47 cases, respectively, in 100000 people and from the cities, Gaz Harbor had the most rate [22].

Shoraka et al. obtained the rate of 25.2 and 38.2 in 100000 people infected with the diseaseinManeh and Samalghanaz cities of Northern Khorasan Province in 2009 and 2010, respectively [23].

Ismaiilnasab et al. (2007) in a study on the patients in Kurdistan Province, estimated prevalence rate of 73.5 in 100000 people [24].

In a study in Kashan in 1997, Malta fever prevalence was reported 0.09% with most people in high risk group. In a Brucellosis seroepidemiology survey in Talesh city, 0.04% prevalence rate was reported which was very high respect to city population [25]. Regarding direct relationship between the disease and livestock in the area, Yazdanpanah et al. conducted an essay in 1994 and recorded contamination rate of 6.62%, which were including ranchers, butchers and veterinarians [26].

An assay was conducted in Yazd Province among blood donors in 2012 which indicated that 6.3 donors were diagnosed with positive blood tests; a rate is no longer negligible [27].

In an assay in Bushehr Province among blood donors in 2009, no one in 10500 patients diagnosed with active disease [28].

4. Symptoms

Clinical symptoms of Malta fever are different dependent on contaminating type of Brucella [29].Human Brucellosis has always animal origin and is transmitted via contact with infected animal e.g. skin and mucosa contamination with Brucellosis infected animal's secretions and embryo. Frequently it is

encountered with indirect transmission via drinking contaminated, unpasteurized milk or dairy products or even fresh cheese as one of the most important infection sources of human brucellosis. Human may infected by *B. melitensis, B. abortuaand B. suis*. It has been reported other brucellosis just in infections with *B. canis* in laboratory technicians and ranchers [10].

In a human, the disease is appeared with acute septicemia and accordingly, there may be long chronic stage event. Brucellosis may no longer cause to abortion in human but it is accompanied by fatigue, joint pain, headache, back pain, raging fever, sweating and etc. The way to enter bacteria in human brucellosis is via digestive system (swallowing milk and other infected dairy products) especially pharyngeal mucosa. Direct contact with skin and mucosa can infect humans. Bacteria entry in animals is via mouth, nose, throat or genital mucosa [7].

Regarding *B. abortu*resistance against bovine polymorph nuclear neutrophils (which is a kind of acute symptom) Caning et al. (1985), Brathram and Caning (1986) have undertaken attractive studies. From these studies, it has been indicated that there are two preventive materials, separated via chromatography, influencing on *B. abortu* culture. These preventive materials with molecular weight less than 1000 are similar with nucleotides and prevent protein iodation by bovine polymorph nuclear neutrophils. Additionally, this degranulation prevents the effect of rimosane on these cells. Protein iodation is a way to measure myeloperoxidase and H_2O_2 released from neutrophils. Therefore, brucella extract intervenes in myeloperoxidase activities and H_2O_2 produced with neutrophils and by this way, it may be secured against destruction in the cell. This type of preventing neutrophil activities is directly dependent on brucella extract. This extract prevents disembody primitive (azurophilic and peroxidase positive) granules. Therefore, when leucocyte granules are no longer emptied, their contents of enzymes released not at all to detrimentally affect bacteria [8].

Brucella extract has a limited effect on secondary (specific or peroxidase negative) granules. Preventing protein iodation is in a close relationship with releasing primitive granules but it isn't dependent on secondary granules disembody. Low molecular weight brucella extract prevents swallowing staphylococcus aureus and Nitro Blue tetrazoliumtest, not at all. Therefore, during infection with *B. abortu*, some neutrophil activities including bacteria swallow remain intact but the bacteria can survive inside these cells and this is because of myeloperoxidase release prevention [9].

Early bacterial reproduction or influx is developed via lymph ways and the bacteria replaced with regional lymph glands. Usually, brucellosis is encountered with phagocyte macrophages but in some special conditions, they can survive inside the macrophages. For example, B. abortu is optional intracellular bacterium which can survive inside macrophages and epithelial cells. Disease latency duration is usually variable between 7days to 21days, although it may prolong to multiple months from infection to early onset of apparent symptoms. Disease onset is frequently sudden, there always is mediate fever in patient and there are no apparent local symptoms in the body [30]. Early onset of clinical symptoms is accompanied by complaint about headache, general weakness, insomnia, sweeting, constipation, back pain and eventually general pain throughout the body. After a while, most patients have no appetite and weight loss, cough, pain behind eyes, paint in joints and limbs and confusion in some rare patients are observed [31].

Bacterial endocarditis resulted from brucellosis, although rare, is one of severe side effects of the disease should be taken consideration. Among other secondary side effects reported rarely in brucellosis infected humans are, in addition to endocarditis, lung abscess, purulent pleurisy, nephritis, osteomyelitis, septic arthritis, pyothorax, optic neuritis and finally meningoencephalitis [31].

In some animals (no human), the bacteria might enter the milk via mammary glands and waits until severe proliferation and ready to appear its specific sign, abortion. Thus, it infects the bovine and swine placenta and finally resulted in abortion.

In animal placenta encountered with abortion, there are much redundant 4-C alcohol sugar named Erythritol which is a very strong stimulant agent of B. abortu, B. melitensis and B. suis growth. Consequently, the bacteria enter epithelial cells of placenta, the placenta will swollen and finally, it can no longer hold the embryo and makes abortion [30].

5. Laboratory diagnosis

For diagnosis, methods including culture and serology are implemented which the latter is more important and prevalent. Serologic tests means testing blood serum of the patient in order to find antibodies against brucellosis, the most important of which are Wright, ME2 and Wright-Coombs tests. This disease is observed clinically in acute, sub-acute and chronicversions. In early weeks of acute stage, IgM antibody is gradually increased and reaches to maximum level within 13-21 days. Early in this stage, 2ME test is negative but the others are positive. Then, IgG production against brucella begins and within multiple weeks, its titration rate will be more than that of IgM. At the end of this stage, all serologic tests to diagnose brucellosis will be positive. During 4^{th} to 8^{th} weeks of acute stage, IgG titration will reach to maximum level and IgG titration, while inappropriate

treatment, will be decreased but IgM titration may be continued for 6 months to 2 years and will be usually decreased every 3 months. If antibody titration decline is observed, it will be a sign of effective treatment and disease subside. Now, if the disease treated incompletely or no longer treated, the disease enters chronic stage. In this stage, antibodies are frequently of IgA, IgG4 and IgG3 types, called blocking or incomplete antibodies [31].

6. Wright test

The test is named after its discoverer. The test is conducted to confirm antibodies against brucellosis in patient's serum. Initially, a rapid test is obtained in which Rose Bengal (containing brucellosis antigen) is used. Having encountered patient's serum with Rose Bengal, a mass resulted from interaction between antigen and specific antibody is produced visible with naked eyes. This reaction between antibody and antigen is generally called agglutination. If this test is positive, titration or Wright test will be implemented to measure antibody titer level. Here, the serum will be diluted by normal saline in 1/20, 1/40, 1/80, 1/160, (the denominator will doubled and this will be continued dependent on positive rate of Rose Bengal) proportions in multiple test tubes. Then, Wright specific tubular antigen is added to each of tubes and they will be incubated at 37°C for 24hr. After that, the tubes will be evaluated regarding agglutination. The last dilution in which agglutination is observed is considered as Wright titration for the patient. In Iran, 1/80 or higher titration is accounted positive but also, 1/20 and 1/40 titrations should no longer neglected in non-occupational disease [32 and 33].

7. 2ME test

2-mercapto ethanol (2ME) test is conducted after positive Wright test to recognize antibody class. In this test, disulfide ligaments in IgM structure and then, total probableIgM's in patient's serum are initially destructed by 2ME. Afterwards, with this serum without IgM, the test will be continued as in Wright test (different dilutions) and finally, 2ME-specific antigen will be added to all tubes. After 24hr incubation at 37°C, the last tube observed with agglutination is reported as 2ME titer. The most important applicability of this test is differential diagnosis between active and inactive brucellosis in a person who has clinical symptoms but with negative culture and low Wright titer. It has been said that in active brucellosis, IgG will be increased (after third week of disease until appropriate treatment) even more than IgM, a situation in which 2ME test is positive but if appropriate treatment is implemented (brucellosis is made inactive), because of IgG destruction, 2ME test will be negative. Of course, at it has been discussed, at first stages of disease when no IgG has been produced, despite of active disease, 2ME test is negative [32 and 33].

8. Wright-Coombs test

This test is conducted when patient entrance in chronic stage is suspected by respective physician. It has been said that in chronic stage, blocking or incomplete antibodies are increased. Among properties of these antibodies is that they can no longer cause to agglutination in reaction with brusella antigens so they called incomplete. In order to these antibodies, having conducted Wright test as indicated before (after 24hr incubation at 37°C)the tubes in which has occurred agglutination not at all are investigated regarding incomplete antibodies. It is known that if these antibodies are in the patient serum, they will react with Wright antigen but this isn't observable. In order to achieve visibility, antibodies are implemented able to connect the tail of antibodies (the head of antibodies is connected with antigens) and this can cause to link adjacent antibodies and finally, agglutination will happen by means of these antibodies. These antibodies are called Comboos serum applicable in some other tests such as diretComboos, indirect Comboos and Cross Match, also in ELISA , blood culture and complement fixation tests 33 and 34].

9. Treatment

Having obstructed the disease by blood test, the treatment is composed of and initiated by a period of bed rest, antibiotics and cortisone medications to decline inflammatory responses and also analgesics to relieve muscular pains whereas all of mentioned treatments should be under the supervision of the respective physician.

10. Adults

1. Rifampin: single 600-900mgr (2-3 300mgr capsules) daily dose, 1hr before meal (fasting) or 2hr after meal for 8 weeks; doxycycline: two times a day 100mgr oral doses;
2. Tetracycline: 500mgr oral doses every 6hr for 8 weeks; streptomycin: 1gr intramuscular dose (750mgr dose should be used to prevent hearing problems in over 50 years old elders); or gentamycin: 3-5mg/kg intramuscular doses every 12hr; side effects should be considered (Note: select one of alternatives for 2-3 weeks).
3. Rifampin: single 600-900mgr (2-3 300mgr capsules) daily dose, 1hr before meal (fasting) or 2hr after meal for 8 weeks; cotrimoxazole: two oral tabs 2-3 times a day.

11. Pregnancy

Treatment is similar with adults with cotrimoxazole + rifampin except that rifampin is transcribed just in first and last months of pregnancy. Treatment duration based on cotrimoxazole+ rifampin consumption is at least 8 weeks.

12. Lactation

Cotrimoxazole should be prevented in first 4 weeks in lactating women and other standard treatments are allowed in other lactation months.

13. Children

10mg/kg or 2drops/kg fasting rifampin for minimum 8 weeks; cotrimoxazole: 8mg/kg based on trimethoprim.

The most important brucellosis prevention way in humans and decreasing economical side effects of livestock is to control disease in sensitive livestock, lambs, goats, sheep, calves, cows and buffaloes vaccination, training executive personnel and extended training in rural and tribal communities, supervision on the operations by sampling and testing, healthy activities, quarantine, tests and measures in slaughters [36].

In developed countries, brucellosis transmission via foods is at minimum level because of milk pasteurization and B. abortu eradication. Now, this disease is accounted an occupational disease in developed countries infectinf people like ranchers, farmers and slaughter personnel. This is while this disease is an endemic and native disease in developing countries which its main transmission way is via animal infected tissues, unpasteurized milk and dairy products. It is surprising that these bacteria survive during different stages of cheese production and can live for months within various hard cheeses. On the other hand, considering that Malta fever bacteria has a long life in ice cream and cream, it is appeared that ice creams are one of main hidden contaminations for Malta fever. Also, consumption of infected meats which are incompletely cocked may transmit the disease to humans.

14. Prevention

Based on a universal standard, Malta fever prevalence in a country is to a large extent related to animal brucellosis prevalence which magnifies the requirement for controlling and eradicating the disease within livestock communities.

Nowadays, brucellosis prevention is done applying two types of live vaccines in cattle and sheep. In order to prevent this disease in humans there is no vaccine in most countries but B. abortu vaccine is available in France. Therefore, the single activity to prevent the disease is to consider health notes in order to prevent the contact with infected animals and also consumption no unpasteurized milk, cheese and other dairy products. By the way, it is recommended that before any consumption, milk should be boiled on direct heat of flame for 15-20min such that during this time, the milk is boiled for minimum 10min. it should be noted that brucella bacteria available in milk is able to link easily with fat particles and transferred on them. In these situations, removing milk cream and consuming it is among main ways to transmit Malta fever. However, brucellosis in Iran is considered as one of dangerous and important diseases common between human and livestock and it is no longer eradicated in human communities without remove, eradicate and control the disease in animals. Of course, any activities with this regard should be according cultural, economic, social and health conditions [35 and 36].

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