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Brucellosis and Its Treatment: An Overview

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ABSTRACT

The facultative intracellular transmitted Bacteria is the Brucella bacteria which is mainly non motile, non spore forming and gram negative bacteria , named after the microbiologist David Bruce in (1855-1931). This bacterium primarily spreads between various type of infected animals to human and the disease is called Brucellosis.This pathogenic zoonoses bacteria has various specises of which most infectious for human's is Brucella melitensis primarily affects camel, goat ,sheep. Again Brucella abortus, Brucella canis, Brucella suis infects hogs,cows,dogs and also others animal's. When this zoonoses bacteria is transmitted in Human's body then it infects our multi organ system specially respiratory, genital system and digestive system. This intracellular pathogen accumulated in the cells and organs of human by the microphase mechanism typically in liver and spleen. The general mechanism of human cell phagocytosis can kill 90-95% of Brucella bacteria after getting internalized by microphages but still few bacteria remain alive which is enough for replication into the host cell.

Keywords: Intracellular Bacteria, Brucella, Zoonoses, Pathogeenic Disease , Non Spore Forming

Introduction

Brucellosis is the generic name used for infections in animals and humans caused by several species of the genus Brucella, mainly Brucella abortus, B. melitensis and B. suis. Brucella infection in cattle is usually caused by B. abortus, less commonly by B. melitensis, and sometimes B. suis. Brucella melitensis is the primary causative agent of Brucella infections in sheep and goats **[1].**. Infection in Brucella pigs is caused by B. suis 1-3 biovars, but the disease caused by biovar 2 differs in host range, limited geographic coverage and pathogenicity. In some areas, infection with B. suis was found in feral pigs. Clinically, Brucella infection in animals is characterized by one or more of the following : abortion, placental retention, orchitis, epididymitis and, less commonly, arthritis, with microbial excretion in uterine and milk secretions. An unequivocal diagnosis depends on the isolation of Brucella from the abortion material, udder secretions, or tissue removed during dissection. Since B.abortus, B. melitensis and B. suis are highly pathogenic to humans, so they potentially contaminatetissues, cultures and materials must be handled under appropriate conditions **[2].**This Bacteria is a harmful pathogenic zoonotic **[3]** intracellular proteobacteria (Gram-negative bacteria)which infect the cells of human-being, **[4].**The term 'zoonosis' can be described as an infectious disease caused by microorganisms that transferred or jumped from animal to a human being.Brucellosis mainly occurs from the domestic animals like sheeps,pigs,rams,cows .This zoonotic bacteria, Brucella consists of total seven species in which*Brucella melitensis*, *Brucella abortus*, *Brucella canis*, *Brucella suis* are known to induce human disease whereas on the other hand,*Brucella neotomae* and *Brucella ovis* are not harmfulfor the human being [5]. Among various species of this zoonotic bacteria*Brucella melitensis*, *Brucella abortus* show prominent attack,which mainly infects the multi organ system of the body includingrespiratory and genital system in both human and animal [6].Thesymptoms include joint infection, fever, cough, cold and its virulence depends on the duration of infection [7].Brucellosis is also known as 'malta fever' or 'undulant fever' [8].WHO declared this diseaseto be the most common in every parts of the world [9].

Symptoms and Signs

The patient had multiple acute symptoms and 4,444 signs of human brucellosis, such as wave fever, myalgia (Table 1), and other clinical symptoms such as spleen enlargement, hepatomegaly, and spondylitis. Infective endocarditis, although rare, is the most serious complication of systemic brucellosis and may require surgery.This is a harmful zoonotic disease [10]for human and animal both [11].The Primary symtoms of brucella is respiratory infection, digestive infection, genital infection but it may be change as per duration of time of the brucellosis infection [12]. As per WHO there are several infection present in Brucella like as join pain, fever , back pain, weight loss, anorexia, fatigue, arthralgia **[13].** As per WHO Table 1 : reports symptoms and sings in 500 patient with brucellosis due to brucella melitensis [14].

Table 1 : Symptoms and signs in 500 patients with brucellosis due to B. melitensis.

Symptoms and Signs	Number of Patient	Percentage (%)
Lack of energy	473	95
Fever	464	93
Aches	457	91
Sweats	437	87
Arthritis	202	40
Chills	410	82
Abdominal pain	225	45
Cough	122	24
Headache	403	81
Joint and back pain	431	86
Testicular pain/epididymo-orchitis	62	21
Loss of appetite	388	78
Diarrhoea	34	7
Sleep disturbance	185	37
Pallor	110	22
Cardiac murmur	17	3
Spinal tenderness	241	48
Weight loss	326	65
Central nervous system abnormalities	20	4
Hepatomegaly	97	19
Constipation	234	47
III appearance	127	25
Splenomegaly	125	25
Jaundice	6	1
Lymphadenopathy	160	32
Rash	72	14

Diagnosis

Diagnostic tools for brucella inculdes isolation and identification of Brucella from clinical sample, detection of genome, antigen and antibodies [15].

1.Culture: Blood cultures mainly provide the solid evidence of brucellosis, but do not provide positive results for the all patients. Dissolved centrifugation and thrombus culture techniques have calculated promising results in terms of sensitivity and rapidity **[16] .** The latest automated blood culture system has slightly improved detection speed. Poor quarantine of thisBacterial techniques in blood culture are impractical for routine diagnosis.

2.Antigen detection: The antigen detection method with the help of enzyme-linked immunosorbent assay (ELISA) [17] is potentially useful and several recent antigen detection systems are under development.

3. Genome detection: The polymerase chain reaction (PCR) [18]was sought for rapid detection and confirmation of Brucella. The technology of molecular properties is Brucella spp. Is a very useful tool for distinguishing follow-up tests, especially for abnormal phenotypic results . The supply of equipment and reagents is a limitation of this technology [19].

4. Antibody detection: Due to the limitations of the above tools, the serum indicated for antibody detection is the most useful tool. Antibodies generally begin to appear in the blood at the end of the first week of infection [20].

(A) Genathering Test

Testing Bengal Rose Plate (RBPT) is one of the experiments called Brucella buffer antigen tests called the principle based on the principle that the ability of IgM-related antibodies [21] , low pH Value is marked**.** It takes place on glass slides with antigen color bacteria, and this test is as a screening test, especially in rural areas at high risk, which is not able to show SAT **[22].** . Whenever possible, a serum brings positive results, so that is confirmed by a more specific test. RBPT **[23]**also plays a big role in the fast confirmation of neurobrucellose, arthritis, curingitis and hydrocele from Brucella. The test is an excellent screening test , but can be overdown to diagnose in each animal, in particular vaccine rates **[24].**

Serum agglutination test (SAT) remains the most popular and globally used diagnostic tool. SAT measures the total amount of agglutinating antibodies (IgM and IgG) **[25]**and is determined by the amount of specific IgG 2mercaptoethanol (2ME). IgG antibody is considered a better indicator of active infections, and the type of antibody is important because a sharp decrease in IgG antibody levels is a prognosis for successful treatment **[26].** This test is easy, cheap to run, but lacking in sensation.

The complement binding reaction (CFT) is a complex method that, although sensitive and specific, requires excellent laboratory facilities and skilled staff. If these are available and tests are run regularly with sufficient attention to quality assurance, it can be very satisfactory reaction test **[27]** .

(B) ELISA Test

The ELISA test provides excellent sensitivity and specificity while being robust and very simple to run the with minimal equipment and is readily available from many commercial sources in kit format. Compared to SAT, ELISA **[28]**offers high sensitivity and specificity. It is reported that the ELISA is the most sensitive test for the diagnosis of neurological brucellosis **[29].** The omp28 protein is currently used in an indirect plate ELISA system and has been evaluated for its excellent sensitivity and specificity in a number of clinical samples.

Fluorescence polarization analysis (FPA) requires special reagents and readers and is known to have advantages over other methods in sensitivity and specificity **[30].** However, evaluation is limited to ,and the procedure is not widely available. More information is needed before evaluating the overall value .This technique is readily applicable to the detection of either the antibody or antigen through simultaneous changes in rotational speed **[31] .** Diagnosis of Brucella disease by test using S phase, Rose Bengal plate test (RBT) serum aggregation test (SAT), comb antiglobulin, complement binding test (CFT), ELISA. **[32].**The results of combining tests such as the SAT or comb antiglobulin can be used to evaluate the steps in disease progression at diagnosis. ELISA with the appropriate IgM or IgG specificity of and a conjugate of SLPS (lipopolysaccharide) can replace the established test, but new standardization and validation are required. Other methods are useful, but have low specificity and are not sufficiently evaluated **[33].**

Protein Diagnostics Test

Antigens of proteins that are important to gin can be classified into four groups: LPS, external membrane proteins, peripheral cytoplasmic proteins, and cellular proteins. **[34].**

- **i)** **LPS:** Smoothness Attention LPS consists of a core area containing lipidA and mannose, Quinova Social Democrats, 3DeoxyDmannose2octulosonate (KDO) and the offside chain **[35]**
- ii) **Outer membrane protein:** Brucella spp. Major outer membrane proteins (OMP). was first identified in the early 1980s and was characterized by potential immunogenicity and protective antigens. OMPs are classified into Group I (88-94 kDa), Group II (35-39 kDa) and Group III (25-31 kDa) proteins based on the mass of the molecule. These proteins feature additional monoclonal antibodies, a) lipoproteins (Omp10, 16, 19), b) two homologous groups (Omp25, Op31), c) folliproteins (Omp2a / 2b), d). Contains Group 1 protein (Omp1) **[18].iii)Periprasm Protein:** Many immunogenic proteins have been identified in Peripurazumu space, such as BP26 and Cu/Zn SOD. **iv)Cytoplasmic Proteins:** Proteins in this category include heat shock proteins DnaK, HrtA, GroEL, GroES and ribosomal L7/L12 proteins **[36].**

Prevention

To prevent human brucellosis alawys avoid consuming milk derivatives and unpasteurized milk. **[37].**Barrier precautions for endangered hunters and professionals (butchers,farmers, slaughterers, veterinarians) **[38].** Carefully handle postpartum and disposal, especially in 4,444 abortion cases. Serological or other tests of animals; vaccination of unreasonable / herd may be expected. Remove infected herds / herds. Occupational and food hygiene; Vaccine is generally not recommended **[39].**

Treatment

Brucella is a pathogenic bacteria mainly four species which are more pathogenic for human body like as *Brucella melitensis*, *Brucella suis*,*Brucella abortus*, *Brucella Canis* and this species are highly infectious by aerosoles **[40].**Human to human transmission does not usually occur.The incubation time/period varies from 5 days to 6 months **[41].** According to durstion of infection symtoms includes fever, joint pain, cough etc. There are variouse combination treatments with Doxycline along with Streptomycin and Refampicin or any amino glycosides act as fisrst line therapy for the treatment of Brucellosis for first six weeks **[42].** Anothers Combination therapy is Tetracycline and Streptomycin also use for the treatment of Brucellosis **[43].**

Name of Active Substance ***Role in Therapy and Prophylaxis***	**Section**	**Treatment of Suspected or Confirmed Clinical Case** Duration Treatment 6 Weeks	**Post Exposure Prophylaxis in case of suspected or confirmed exposured to the pathogen** Duration Treatment 3 to 6 Weeks
Doxyxline use to first line treatment combination with gentamicin or rifampicin in adults and children, children age above 8 years old. First line prophylaxis in combination with refampicin in adults and child more than 8 years of age	**Posology**	**For Adults** 100mg iv twice daily 100mg orally twice daily **For Children** >8years and >45kg Adult dose >8 years and<45kg 2.2mg/kg iv twice daily and same for oral dose	**For Adults** 100mg orally twice daily **For Children** >8years and >45kg Adult dose orally >8 years and<45kg 2.2 mg/kg orally twice daily
	Contraindication	Should be considered in view of the prescribing information given in the different	
	Pregnancy and lactation	Given only the seriousness condition	

Table 2 : Combination Medication Treatment and Their Dose . [44-49]

Name of Active Substance ***Role in Therapy and Prophylaxis***	**Section**	**Treatment of Suspected or Confirmed Clinical Case** Duration Treatment 6 Weeks	**Post Exposure Prophylaxis in case of suspected or confirmed exposured to the pathogen** Duration Treatment 3 to 6 Weeks
Refampicin use to first line treatment combination with doxycyline adults and children, children age above 8 years old. First line prophylaxis in combination with doxycycline in adults and child more than 8 years of age	**Posology**	**For Adults** 10-15mg/kg iv daily 600-900mg orally daily **For Children** 10-15mg/kg iv daily 10-15mg/kgorally daily	**For Adults** 600-900mg orally daily **For Children** 10-15mg/kgorally daily
	Contraindication	Should be considered in view of the prescribing information given in the different	
	Pregnancy and lactation	Given only the seriousness condition	

There are another alternative theray also present like combination therapy of sulfamethoxazole -trimethoprim and combination with ofloxacine or ciprofloxacine also used as a first line therapy for the treatment of brucellosis **[50].**

Conclusion

Brucellosis has been eradicated in many developed countries, but remains an important public health problem in most developing countries due to the serious economic losses associated with abortion and unreasonable infertility. Human brucellosis is commonly reported among laboratory workers, slaughterhouse employees, farmers and veterinarians who can be exposed to infected animals.For its non-uniformity and lack of specificity, the diagnosis of Brucellosis has always required laboratory conformation, either by isolation of pathogen or demonstration of specific antibodies. The serological test available for the diagnosis of Brucellosis continues to be the most useful test for preliminary identification of the disease, as well as the limitation of for its low sensitivity.Therefore, it is necessary to develop a fast, reliable and user-friendly system for the diagnosis ofdiseases and alternative vaccine access. Because of the inherent challenges of in isolation, inefficiency, cost, risk, and other factors, most laboratories prefer to use other, more cost-effective methods. As a diagnostic tool, molecular biology is advancing and is soon to replace actual bacterial isolation. It's fast, safe and cost-effective, and the only real problem is some uncertainty about specificity.

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