Journal of Veterinary Pathology Research

Kosha BK, J Vet Pathol Res 2022, 3:1

Review Article Open Access

Canine Brucellosis: Insight on Pathogenicity, Zoonosis and Diagnostic Aspects

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: Pathogenesis, Microbes, Veterinary Microbiology, Aerobic, Infection, Gram Negative, Gram Positive, Diseases.

Brucellosis is a severe febrile disease caused by various members of the genus Brucella. It is a worldwide problem, causing abortion and infertility in domestic and wild animals [1]. Brucella is aerobic, small, Gram-negative rods and is oxidase, catalase, and urease positive. Brucella, a genus discovered in 1887 by David Bruce, contains the following species: Brucella suis, B. ovis, B. abortus, B. canis, B. melitensis, B. neotomae, B. ceti, B. pinnipedialis, B. microti, B. inopinata, B. papionis, B. vulpis and other strains obtained from environmental samples [2]. Brucellosis in dogs occurs worldwide and is endemic to America, Asia, and Africa. ere have been many reports of brucellosis outbreaks in the canine populations a er 1966 which has led to infertility and abortion in dogs.Brucellosis can be transmitted from dogs to humans as well as from human to human also. Brucella rods enter the host cells by inhalation, ingestion, skin abrasions, through mucous membranes [3]. A er penetration into host, the rods multiply in lymph nodes a er which, they penetrate other organs. Brucella can modify immune response in host cells due to its a nity to speci c tissues, e.g. placental trophoblast in fetal lung, pregnant females or reproductive system. Brucellosis causes enlargement of lymph nodes, liver and spleen. Pathogenicity of Brucella is dependent on their ability to multiply and survive within macrophages. In this review we call attention to brucellosis in dogs, highlight the Brucella canis as an unidenti ed pathogen and trace the present cognition regarding its zoonotic potential.

rucella spp. is frequently called as „„nasty bugs"" based on their unusual virulence characters. Brucella canis has expertise to live and grow inside phagocytic and non-phagocytic cells. Virulence factors of Brucella are not classical: exotoxin, cytolisins, exoenzymes, plasmids, mbriae, and drug resistant forms. e signi cant virulence factors are: lipopolysaccharide (LPS), T4SS secretion system and BvrR/BvrS system, which allow association with host cell surface, formation of an early, late BCV (Brucella Containing Vacuole) and relation with endoplasmic reticulum (ER) when the bacteria proliferate.

: LPS is a crucial virulence factor of Brucella and consists of lipid A, an oligosaccharide core andO-antigen. eLPSisdi erentandnon-classicalin Brucella as compared to other Gram-negative bacteria like E. coli. e LPS is comparatively less toxic and less active than the classical LPS which cause a high fever. While non-classical LPS observed in B. canis causes a low fever, being a weak inducer of tumor necrosis factor [4, 5].

(4): T4SS is a multi-protein compound involved in production of bacterial macromolecules. VirB operon encoding 12 proteins characterize this system (11, 860 bp). Expression of the virB operon is regulated by the regulator of quorum-sensing – VjbR. Where wild strains of Brucella can proliferate only in the endoplasmic reticulum, VirB mutants of Brucella cannot multiply within the endoplasmic reticulum due to its incapability to reach the ER, or multiply within [6]. In the macrophages, Brucella rods are localized

chronic epididymitis and orchitis may lead to unilateral or bilateral atro
late term abortion accompanied by inodorous, brown to yellow genital
edematous, congested with hemorrhages in the subcutaneous abdomin
that may die within few days. Various serological diagnostic tests ha
available. Isolation of bacteria from blood samples is considered as go
have also been developed with varying sensitivity and specifcity. Do
infection is acquired by direct contact with infected dogs or their bloo
nonspecifc fu like and include fever, headache, back pain, chills/nigh
misdiagnosed. Unlike dogs, human do respond well to antibiotic therap
The disease burden can be reduced by preventing unrestricted movem
of breeding animals and their ofspring before sale. Sterilization of inta
limit the disease spread as well as the level of infection in canine popu

is responsible for formation of specialized brucellae- multiplication compartment. e attainment of endoplasmic reticulum membrane is controlled by functional virB secretion system – T4SS.

: Macrophages containing Brucella produce reactive oxygen intermediates (ROIs), which is a primary mechanism of destruction of the ingested bacteria and also prevents their intracellular replication [7]. e main line of defense that prevents reactive O2 intermediates includes superoxide dismutase and catalase. SOD (metalloenzyme) is encoded by sod sequence and includes iron, magnesium, or zinc and copper at its active site. SOD is accountable for dismutation of O2– (superoxide) to H2O2 (hydrogen peroxide) and O2 (oxygen) – transfer from one molecule to another (2O2+2H+ →H2O2 +O2). Catalase breaks down hydrogen peroxide into oxygen and water. Catalase activity is limited to the periplasmic space, where together with Cu-Zn SOD leave external sources of ROI unchanged. Catalase is not a necessary virulence factor; the other enzymes can compensate lack of this enzyme in catalase mutants, e.g. alkyl hydroperoxide reductase or enzymes involved in DNA repair mechanisms.

C -1-2- (C): Brucella CβG belongs to II OPGs (Osmoregulated periplasmic glucans) family [8]. ese glucans engage in direction of the phagosome- lysosome fusion. Mutants are killed in phagolysosome and they are not allowed to grow. Even more, mutants treated by CβG are good to determine vacuole maturation and lysosome fusion, so they can contact the ER and replicate there. Brucella has non-identical urease operons in two distinct genomes. Urease is a metalloenzyme which destroys urea to carbonic acid and ultimately breaks it down into the ammonium form, which increases the pH. is ensures it's persistent in the acidic environment [9]. In chromosome I, there are two urease-operons: ure-1 and ure-2, separated by 1 Mb of DNA. Ure-1 and ure-2 encode structural genes: ureA, ureB, ureC and accessory genes: ureD, ureE, ureF, ureG. Urease may pre(y p)12(e(y p)12a(t)6(a)9 (ni)3 (sm)n ( )]TJ0.106s U)43geosomoca(t)6(ae s)5 (t)-5 (r)-osome..14 (a)5 (nsw 0 -1.2 Td3ge)-5 (r)-es:ae pH.

viscous and serosanguinous vaginal discharge can last for 1–6 weeks a er abortion.

e most common gross lesions are observed in the lymph nodes and spleen with variable degree of swelling. e testes show marked swelling with multifocal to di use reddish discoloration. In some male dogs, epididymal swelling and scrotal necrosis have also been observed. Non-pregnant female dogs do not show any speci c gross lesions. However, an aborting bitch shows brownish vulvar discharge. Aborted fetuses are o en partially autolyzed with a brown or greenish-gray placenta. ere are also di erences in the lungs between adult dogs and aborted foetuses where the changes in the lungs are much less prominent as compared to the ndings described for adult dogs having brucellosis [16]. Previous studies have shown that histological alterations in the lung are the most signi cant lesions in aborted fetus.

Mild to severe lymphohistiocytic interstitial in ammation is observed in the prostate glands of male dogs su ering from B.canis. Scrotal dermatitis characterized by the in ltration of lymphocytes and neutrophils with epidermal ulceration or crust formation has also been observed in some male dogs. e mammary gland shows multifocal interstitial lymphocytic in ltration in female dogs along with multifocal-to-di use lymphoclaN2 (m B)17 (4m)4 (e)0.5 ronilahgiw 0 -1terahhgiale drlc2 (t)-5 .1 (t)(c)antaneth19 (p f)9 (o(h)3 (a) r)13 7hs

where coccobacillary organisms as well as many immune cells were observed containing round or oval shaped bacteria in their cytoplasm. performed Bruce ladder multiple PCR assay using tissue samples from reproductive organs to detect Brucella canis but compared to tube agglutination method, it was shown to be not a de nitive or reliable diagnostic method. evaluated four genes (BCSP31, 16S-23S intergenic spacer region, porins omp2a/omp2b and for insertion sequence IS711) using PCR to detect Brucella spp. isolated from blood and urine samples of dogs and found that gene coding for 16S-23S intergenic spacer region is the best choice in the canine clinical samples. for the rst time developed a species speci c((BcSS) PCR against B. canis infection with a detection limit of 6pg/µl and by using the bu y coat which was 100 times more sensitive than whole blood. [20] evaluated potency of molecular techniques comparing between PCR and LAMP (loop-mediated isothermal ampli cation) assay targeting IS711 insertion sequence to detect B. canis and found to have 100% speci city for both techniques but with 100% and 44.44% sensitivity in PCR and LAMP. Even scientists have tried using related antigen to detect anti-Brucella antibodies in canine blood as sero prevalence study.

Determined the genetic similarity between Rhizobium tropici CIAT 899 strain and Brucella canis NCTC 10854 strain using RAPD-PCR and evaluated feasibility of using R. tropici to detect anti-Brucella antibodies but showed elevated result for false positive and false negative sera as compared to Indirect ELISA using Brucella antigen itself, hence proved to be not feasible.

Developed enzyme (iELISA) and lateral ow immunoassay (LFIA) using rough Lipopolysaccharide antigens of B. canis which was a rapid and easy test that could be used as screening test with high speci city and sensitivity. For both of the developed tests iELISA as well as LFIA, the sensitivity was found to be 98.6%, and the speci city was 99.5% and 100%, respectively. Although now a days matrix-assisted laser desorption/ ionization time-of- ight mass spectrometry (MALDI-TOF MS) is being performed mostly for identi cation of bacteria but it is limited to genus level only. But with combination of genotypic characterization, the species level also can be identi ed for the same [20]. Did genetic characterization and performed MALDI-TOF MS to identify B. canis in blood culture.

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B. abortus, B. melitensis and biovars 1, 3, and 4 of B. suis are associated with zoonoses whereas B.canis is less regarded with zoonosis because of various reasons. First, cross species transmission has been seen in di erent species of Brucella. Second, the disease in humans is under reported and misdiagnosed due to the nonspeci c nature of clinical signs produced and due to inability of the commercially available serological tests to detect rough B. canis bacteria. ird, con rmation of the disease is challenging due to intermittent bacteremia observed in the a ected patients making diagnosis extremely challenging.

Human infection has a low prevalence and is acquired by direct contact with infected dogs or their blood or reproductive products viz. aborted material, seminal uid, vaginal discharge, urine etc. Among di erent samples, farces and vaginal discharge a er abortion contain the highest bacterial load. Pregnant women, children, and immunosuppressed patients among general public and Veterinarians, laboratory workers, dog breeders and animal caretakers/ kennel workers constitute the high risk group. High burden of canine brucellosis in the stray dog population could lead to spill over in humans in areas where intact, stray dogs are taken into shelters or adopted. Pet owners which adopt an infected dog may also be at high risk of contracting the diseases as neutered dogs can still shed the bacteria in secretions and urine.

e disease burden can be reduced by preventing unrestricted movement of reproductively intact dogs by continuous testing of breeding animals and their o spring before sale. Sterilization of intact stray animals and euthanasia of infected dogs may also limit the disease spread as well as the level of infection in canine population.

e general public must be made aware about the importance of proper diagnosis and methods to limit the further spread of infection

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