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Canine Bartonellosis

PROFILE

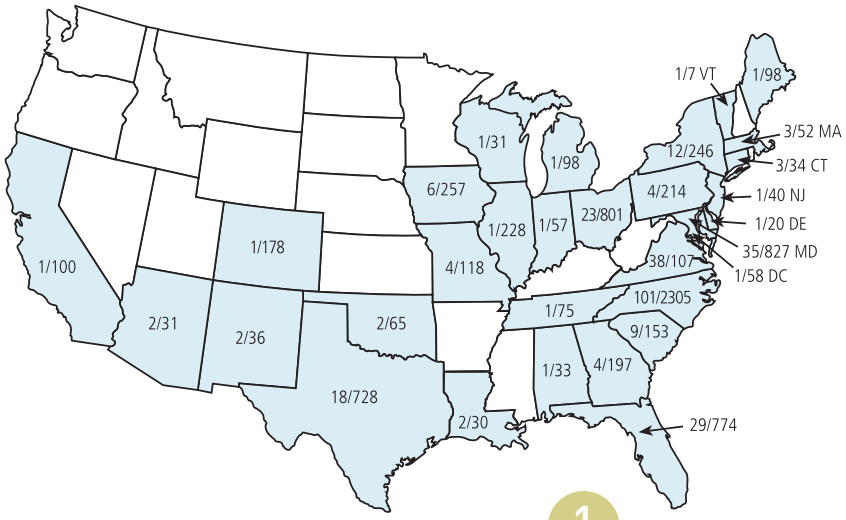
Definition

Bartonella species are emerging zoonotic bacterial pathogens that are of increasing medical importance in veterinary and human medicine.[1-3] Approximately 11 species have been identified as pathogenic for human disease, and 6 of these have been isolated from pet cats and dogs.[1] *Bartonella henselae* and *Bartonella vinsonii* subspecies *berkhoffii* are the most commonly identified species in sick dogs and have been isolated from the blood of immunocompetent human patients.[4]

Systems. These intraerythrocytic, endotheliotropic bacteria have been associated with a spectrum of disease manifestations involving the lymph nodes, heart (valves and myocardium), vasculature, liver, joints, and central nervous system.[4]

Genetic Implications. As is true of other companion animal infectious diseases, a genetic predisposition may exist. *Bartonella* species have been found in 18% of healthy golden retrievers; although U.S. data are scarce, some research suggests that overall seroprevalence is less than 5%.[1,5] In 1 study involving 1872 working dogs owned by the U.S. government, German shepherd dogs were significantly less likely to be seropositive for *B vinsonii* subspecies *berkhoffii* than other breeds.[6] Acquired or therapeutically induced immunosuppression enhances disease expression.

Incidence/Prevalence. Cats are the primary reservoir host for *B henselae*, which is transmitted among cats and potentially dogs by fleas. Canids, including coyotes, dogs, and gray foxes can serve as reservoir hosts for *B vinsonii* subspecies *berkhoffii*, and tick transmission of this subspecies is suspected.[7] In nontropical areas, dogs appear to be accidental hosts for several *Bartonella* species.[1]



1

Bartonella henselae seroprevalence by state based upon tick-borne disease panel results (9030 samples from sick dogs tested from 2004–2007) from the North Carolina State University College of Veterinary Medicine, Vector-Borne Diseases Diagnostic Laboratory. An antibody titer of 1:64 was considered seroreactive, and individual requests for *B henselae* serology are not included in the data summary.

Geographic Distribution. The geographic distributions of the various *Bartonella* species vary greatly (likely reflecting the distribution of their hosts and vectors), but *B henselae* and *B vinsonii* subspecies *berkhoffii* have worldwide distribution. Prevalence is higher in regions where flea and tick infestations are more likely.[1-3,7] On the basis of seroprevalence data, dogs are exposed to *B henselae* and *B vinsonii* subspecies *berkhoffii* throughout the U.S., but some research has demonstrated that *B vinsonii* seropositivity may be more likely in tropical and coastal areas receiving high levels of precipitation.[1,8,9] (**Figures 1 and 2**).

Signalment

Species. *B henselae* and *B vinsonii* subspecies *berkhoffii* have caused endocarditis in dogs and

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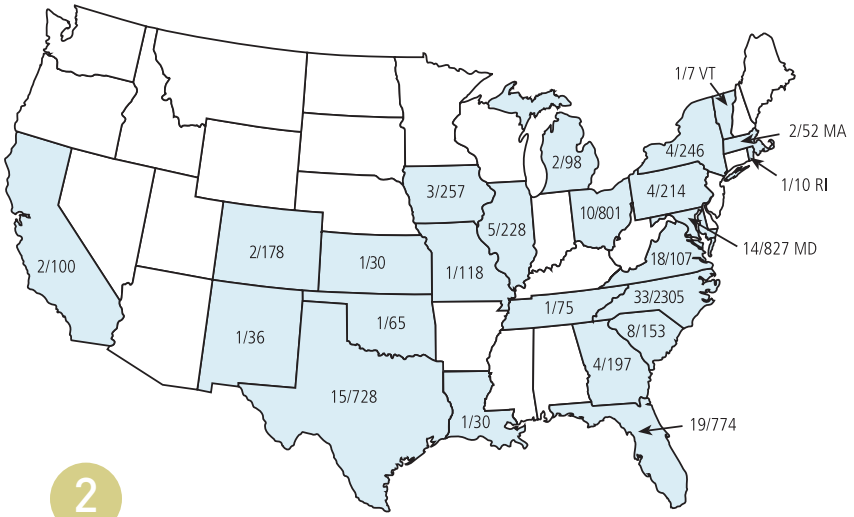


2

Bartonella vinsonii subspecies *berkhoffii* seroprevalence by state based upon tick-borne disease panel results (9030 samples from sick dogs tested from 2004–2007) from the North Carolina State University Vector-Borne Diseases Diagnostic Laboratory. An antibody titer of 1:64 was considered seroreactive, and individual requests for *B vinsonii* subspecies *berkhoffii* serology are not included in the data summary.

people. To date, 7 *Bartonella* species have caused endocarditis in dogs.[4]

Breed Predilection. Epidemiologically, *B henselae* and *B vinsonii* subspecies *berkhoffii* seroprevalences correlate with midsize and large-breed dogs that are allowed to roam.[10,11]

Age & Range. Exposure is more likely in middle age to older dogs residing in rural environments with frequent flea and tick exposure.

Gender. Female sex predilection is suspected in human patients. No sex predilection has been identified in dogs.

Causes & Risk Factors

Bartonella species can be transmitted to humans via a bite or scratch (cat, dog, or rabbit scratch disease). Research in cats has shown that claws contaminated with flea feces are the predominant source of infection, whereas reports of *B henselae* shedding in cat saliva are inconclusive.[1]

Less is known about risk factors for canine bartonellosis, but dogs are most likely infected through animal scratches and bites from fleas, ticks, and other arthropod vectors. In particular, there is increasing interest in the role of tick bites in transmitting *Bartonella* infection because some correlation has been found between high tick burden and *B vinsonii* subspecies *berkhoffi* seroreactivity.[7] Understandably, these bacteria pose an occupational risk for animal health professionals.[12,13]

Pathophysiology

Presumably complex, the pathophysiology of *Bartonella* species infection is incompletely understood.[3,4] Following transmission, bacteria localize to erythrocytes, endothelial cells, and, based upon *in vitro* data, macrophages and dendritic, microglial, and CD34 bone marrow progenitor cells. Lymphoid hyperplasia, granulomatous inflammation in a variety of tissues, vasculitis, and vasoproliferative lesions are among the reported pathologic lesions.

Signs

History. Due to the highly adaptive nature of these vector-borne bacteria, most dogs experience an acute illness that may or may not be associated with fever or evidence of a systemic inflammatory response, followed by a chronic, insidious course of illness spanning months to years. Lameness, intermittent lethargy or fever, epistaxis, and neurologic abnormalities, including lack of coordination or seizures, can develop progressively in chronically infected dogs.[4,14-16]

Physical Examination. Chronically infected dogs may not exhibit clinical signs of illness.[17] Dogs with neutrophilic polyarthritis may exhibit a mild shifting leg lameness or severe debilitating joint pain.

DIAGNOSIS

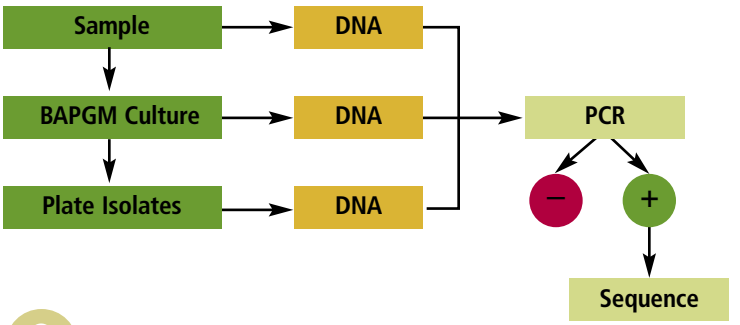
Definitive Diagnosis

As is true for other intracellular pathogens that induce chronic infection in dogs after vector-borne transmission, diagnostic confirmation of active infection with a *Bartonella* species can be extremely challenging. Due to cost and duration of therapy, the diagnosis of bartonellosis should be confirmed by culturing the organism from blood; cerebrospinal, aqueous, or joint fluids; thoracic, pericardial, or abdominal effusions; or tissue biopsy samples.

BAPGM = *Bartonella* alpha-Proteobacteria growth medium; IFA = indirect immunofluorescent antibody; PCR = polymerase chain reaction

PCR Assay

When blood culturing cats, *B henselae* and *B clarridgeae* can be readily isolated; however, isolation from dog, horse, or human blood samples using the same approach is very insensitive.[18] Therefore, to increase diagnostic sensitivity, we combined enrichment culture in a specialized growth medium (designated *Bartonella* alpha-Proteobacteria growth medium or BAPGM) with a highly sensitive polymerase chain reaction (PCR) assay. Currently, BAPGM (galaxydx.com) provides the most sensitive (98% at 1 bacterium/mcL) modality to confirm active infection with a *Bartonella* species in companion animal or human patient samples (**Figure 3**).

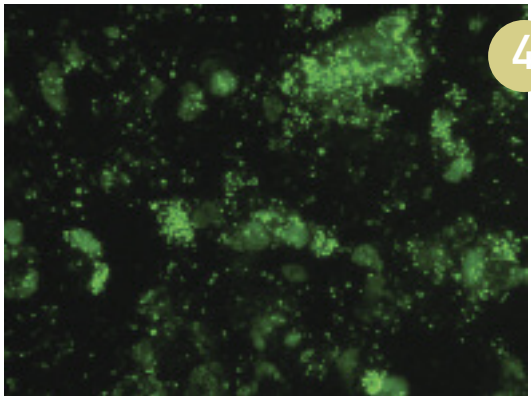


3 A diagram depicting the steps involved in the BAPGM platform. PCR is performed following extraction of DNA from the original patient sample, enrichment incubation in BAPGM, and subculture onto a blood agar plate. BAPGM is a patented insect cell culture-based liquid growth medium that was optimized to facilitate the growth of *Bartonella* species and other fastidious bacteria.[18] The enrichment process increases the quantity of *Bartonella* species DNA so as to enhance the sensitivity of the PCR assay. All PCR-positive samples are sequenced to determine the *Bartonella* species and strain.

Alternatively, PCR can be used to amplify bartonella DNA from paraffin-embedded lymph nodes, heart valves, or other tissues, but PCR with preenrichment culture is reportedly 2 to 3 times more sensitive than direct PCR alone.[19,20] Immunosuppressive drugs appear to increase the quantity of *Bartonella* in blood, whereas administration of antibiotics prior to obtaining samples for BAPGM culture will decrease detection.

IFA Testing

By indirect immunofluorescent antibody (IFA) testing, antibody reactivity to the *Bartonella* species antigens is detected in only 50% of dogs and humans in which active infection with *B vinsonii* subspecies *berkhoffii* and *B henselae* can be documented (**Figure 4**). Therefore, antibody testing in dogs and human patients is insensitive, and, if detected, the presence of antibodies can only be used to infer prior exposure.[4]



4 An example of *Bartonella vinsonii* subspecies *berkhoffii* immunofluorescent organisms (serum antibody titer of 1:2048) using the IFA serologic assay in the North Carolina State University Vector-Borne Diseases Diagnostic Laboratory. The test serum was from a military working dog with *B vinsonii* subspecies *berkhoffii* genotype III endocarditis. Bacteremia was confirmed using the BAPGM platform.[4]

Differential Diagnosis

As intravascular, endotheliotropic bacteria, *Bartonella* species can localize to numerous tissue locations within the body. Bartonellosis would be a differential diagnosis for dogs with endocarditis, myocarditis, polyarthritis, meningoencephalitis, granulomatous inflammatory disease, lymphoid hyperplasia, hypersplenism, epistaxis, idiopathic cavitary effusions, vasculitis, fever of unknown origin, and vasoproliferative lesions. Each of these conditions can be caused by numerous infectious, neoplastic, and autoimmune conditions. Due to the presence of antinuclear antibodies in dogs with bartonellosis, infection with these bacteria should be ruled out in dogs with suspected systemic lupus erythematosus.

Laboratory Findings

Most dogs chronically infected with a *Bartonella* species have no laboratory abnormalities until fulminate clinical signs develop. Then, laboratory abnormalities are nonspecific.[19-22] These bacteria have been isolated from the blood, cerebrospinal fluid, and joint effusion samples from dogs with immune-mediated hemolytic anemia, immune-mediated thrombocytopenia, neutropenia, neutrophilia with a mild left shift, eosinophilia, unexplained hypoalbumenemia, mild hyperglobulinemia, mild to moderate elevations in liver enzyme activities, and hematuria.

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Postmortem Findings

Due to the chronic nature of *Bartonella* species infections, causation has not been clearly established for many pathologic lesions found in culture or PCR-positive dogs. Multiple *Bartonella* species have been associated with endocarditis in dogs. Other pathologic lesions for which these bacteria should be considered include granulomatous lesions of undetermined cause, lymphoid hyperplasia, hypersplenism, peliosis hepatis, and bacillary angiomatosis.[4,23]

TREATMENT

Inpatient or Outpatient

Following diagnostic confirmation of active infection, most dogs can be treated as outpatients. Dogs with severe life-threatening illness, such as endocarditis, myocarditis, encephalitis, immune-mediated hemolytic anemia, or idiopathic thrombocytopenic purpura require intravenous antibiotics in conjunction with intensive monitoring and critical care; temporary immunosuppressive drugs may also be needed to suppress immune destruction of platelets or erythrocytes.

Medical

Antibiotic therapy is needed to eliminate the source of infection; pain management may also be needed. Additional medications are discussed in the following section.

Surgical

Surgery may be required in selected cases to obtain tissue biopsies for histopathology, BAPGM enrichment culture, and PCR.

Activity

Moderate exercise restriction would only be applicable for dogs with endocarditis, myocarditis, or severe debilitating polyarthritis.

Nutritional Concerns

Substantial, unexplained weight loss has occurred in a small subset of dogs in which *Bartonella* bacteremia was confirmed. Feeding a high-quality, high-quantity protein diet should enhance immune function and facilitate antibiotic elimination of infection.

Alternative Therapy

Due to the protracted course of antibiotic therapy that is currently recommended for treatment of bartonellosis in dogs, obtaining a definitive diagnosis is highly recommended. Alternative therapies have not eliminated this infection in dogs, and no alternative therapy has been shown to produce adjunctive affects.

Client Education

Clients should avoid bites, scratches, or contact with saliva from infected dogs. In conjunction with directed medical therapy, clients should apply acaricides to prevent future vector transmission by fleas or ticks.[5,7,10,11]

MEDICATIONS

Drugs

Antibiotics are currently the mainstay of treatment. Because these bacteria can induce intracellular as well as intravascular infection, antibiotics should be dosed to achieve therapeutic drug concentrations within cells and within plasma.

- On the basis of findings from *in vitro* antimicrobial testing, azithromycin, doxycycline, enrofloxacin, and rifampin are effective antibiotics.[24] Due to recently documented treatment failures and evidence supporting rapid development of resistance, azithromycin should be used with caution.[20,25]
- Simultaneous administration of more than 1 antibiotic is necessary to eliminate infection in some dogs. Doxycycline, as a sole therapy, can induce clinical or hematologic improvement but does not eliminate the infection.

Contraindications

Caution should be exercised if there is a history of allergic response to a specific class of antibiotics.

Precautions

Antibiotics used to treat bartonellosis can induce anorexia, vomiting, diarrhea, and increased liver enzyme activities.

Interactions

Many dogs become lethargic and inappetent 3 to 6 days after initiation of antibiotics. Although the cause of this phenomenon is not known, it is presumably due to bacterial death and cytokine release.

TX AT A GLANCE

- Definitive treatment regimens have not been established for dogs.
- Doxycycline (5 mg/kg) and enrofloxacin (5 mg/kg) Q 12 H for 6 weeks.

  or

  Doxycycline (5 mg/kg) and rifampin (5 mg/kg) Q 12 H for 6 weeks.
- If endocarditis is documented, treat initially (1–2 weeks while monitoring renal function) with an aminoglycoside.

BAPGM = *Bartonella* alpha-Proteobacteria growth medium; PCR = polymerase chain reaction

FOLLOW-UP

Patient Monitoring

A complete blood count and serum biochemical profile should be performed 2 weeks following initiation of antibiotic therapy, or sooner if the dog experiences progressive clinical signs of illness.

Complications

Treatment failures are a major complication.

Course

Dogs are treated with antibiotics for 6 weeks; in some dogs, a combination of 2 antibiotics may be necessary to achieve a cure.

Future Follow-Up

To confirm therapeutic elimination of the infection, a BAPGM platform culture/PCR assay should be performed 2 weeks following completion of antibiotic therapy. If the dog is *Bartonella* seroreactive, antibody titers drop rapidly. Most successfully treated dogs will become seronegative within 3 to 6 months.

IN GENERAL

Relative Cost

Diagnostic evaluation, effective treatment, and recommended follow-up to prove therapeutic elimination make this an expensive disease to manage ($$$$).

Cost Key

$ = < $100	$$$$ = $500–$1000
$$ = $100–$250	$$$$$ = > $1000
$$$ = $250–$500	

Prevention

All known *Bartonella* species are transmitted by a spectrum of arthropod vectors, by animal bites or scratches, by blood transfusion from an infected donor, or mechanically by needle sticks.[1-4,7]

Prognosis

Prognosis varies from grave to good, depending upon the disease manifestations and response to antibiotics.

Future Considerations

Since *Bartonella* is a recently discovered genus of bacteria, considerable research is required to define optimal treatment and prevention strategies.

See Aids & Resources, back page, for references and suggested reading.

Dr. Breitschwerdt discloses that he is chief scientific officer for Galaxy Diagnostics (galaxy.com), and developer and patent holder of the *Bartonella* alpha–Proteobacteria growth medium.