


TOP 5

TOP 5 *BARTONELLA* SPECIES OF HUMAN SIGNIFICANCE

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A microscopic image showing numerous Bartonella bacteria. The bacteria are rod-shaped, with some appearing as single cells and others in pairs. They have a yellowish-green outer membrane and a bright red, textured interior. The background is a blurred mix of blue and purple hues.

Bartonella spp are vector-borne, blood-borne, gram-negative bacteria of emerging global health importance in humans and animals, with new species, reservoirs, and arthropod vectors being identified with increasing frequency.¹ In their reservoir hosts, *Bartonella* spp can cause intraerythrocytic bacteremia and endotheliotropic infections that can last weeks to years without resultant disease.² Of the 38 known *Bartonella* spp, at least 17 species or subspecies are known to cause disease in humans,¹ with *B henselae*, *B quintana*, *B bacilliformis*, *B koehlerae*, and *B vinsonii* subsp *berkhoffii* most frequently identified.^{2,3}

TOP 5 *BARTONELLA* SPECIES OF HUMAN SIGNIFICANCE

1. *B henselae*
2. *B quintana*
3. *B bacilliformis*
4. *B koehlerae*
5. *B vinsonii* subsp *berkhoffii*

Clinicopathologic differences of the many *Bartonella* spp are not well-documented,² and factors such as virulence among species and strains, mode of transmission, host immune response, concurrent disease, and immunosuppression may all contribute to clinical signs and degree of disease manifestation.³

Following are the author's top 5 *Bartonella* spp and their significance in humans.

1 *B henselae*

B henselae can be found worldwide,⁴ and although cats are its primary reservoir,^{5,6} other animals (eg, dogs, raccoons, mon-gooses) may also be sources of infection.² *B henselae* is transmitted among cats through flea feces (*Ctenocephalides felis*) and scratches from nails contaminated with flea feces.^{2,4,7,8} *B henselae* transmission to humans from dog bites^{2,9} and cat bites and scratches^{5,6} appears to be a low-risk source for human infection unless the animal is concurrently infested with fleas or the nails or saliva are contaminated with flea feces.² Ticks, spiders, and mites may also play a role in transmission of *B henselae* to animals and humans.^{2,10,11} Bacteremia has been identified in various animals²; in cats (stray or pet), infection prevalence varies considerably by geographic area.⁶ Infection prevalence in cats is highest in warm, moist areas with high flea burdens.^{4,5,12} A North American study found seroprevalence rates to be higher in warmer regions as compared with cooler regions.¹² Overall, 27.9% of cats tested in

that study were seropositive. Bacteremia in cats can be intermittent,¹⁰ occurs primarily in cats younger than 2 years, and can last a year or longer.^{6,7} The seroprevalence rate of *B henselae* in dogs in the southeastern United States has been recorded to be 10% in healthy dogs and 27% in sick dogs.¹³ Broader studies have found 2% to 3.8% of dogs to be seropositive for *B henselae*.^{14,15}

B henselae infection in humans and animals can be subclinical; this is particularly common in cats due to their coevolution with *B henselae*.^{2,7,16} Although association between infection and clinical signs in cats is equivocal,¹⁷ signs can include endocarditis,^{2,6} myocarditis,^{2,7} fever,¹⁸ lethargy,^{3,18} gingivostomatitis,¹⁹ uveitis, conjunctivitis, and others.³ In dogs, *B henselae* can cause fever, endocarditis, granulomatous hepatitis, peliosis hepatitis, lymphadenomegaly, panniculitis, and vasoproliferative lesions, as well as others.^{2,3,5,20}

B henselae is the predominant cause of cat scratch disease (CSD) in humans.^{10,21} There are an estimated 500 hospitalizations and 12 000 outpatient cases of CSD each year in the United States.⁸ In humans, at the site of inoculation, a cutaneous papule or pustule develops 3 to 10 days after contact with an infected animal and may last 1 to 3 weeks.⁴ Accompanying signs may include regional lymphadenopathy, fever,¹⁸ fatigue, malaise, headache, sore throat, and/or rash.⁴ More severe signs may include neuralgia, endocarditis, osteomyelitis, Parinaud's oculoglandular syndrome, pneumonia, hepatitis, splenitis, and/or encephalopathy.⁴ *B henselae* and *B quintana* are causative agents of bacillary angiomatosis, a neovascular disorder that occurs primarily in immunocompromised individuals and involves the skin, lymph nodes, and a variety of organs.^{4,22,23} Although CSD is often self-limiting, *B henselae* can cause chronic or intermittently clinical illness accompanied by persistent bacteremia.²⁴

2 *B quintana*

B quintana, and to a lesser extent *B henselae*, was the causative agent of trench fever during World War I and has recently been

the cause of urban trench fever, which occurs predominately among homeless and marginalized populations.²⁵⁻²⁸ *B quintana* can be found worldwide and is transmitted among humans via feces of the human body louse (*Pediculus humanus*).^{2,26} Humans are considered incidental hosts for all *Bartonella* spp, with the exception of *B quintana*, for which humans are reservoir hosts.^{4,17} New findings, however, support the role of *C felis* in transmission and suggest that cats, dogs, and, possibly, the cynomolgus monkey—all accidental hosts—may also serve as sources of infection.^{2,3,10,17,29,30} *B quintana* transmission to humans has rarely been associated with cat bites and scratches, and transmission from dogs to humans has never been documented.¹⁰

B quintana does not appear to cause illness in cats, despite evidence of infection.^{3,21,31} *B quintana* infection in dogs is typically subclinical but has been associated with endocarditis.^{2,32} Prevalence of these pathogens in cats and dogs is not well-known. A study in Germany demonstrated a *B quintana* seroprevalence rate of 18% in stray cats.³ In a study in Israel, 2.6% of cats were found to be seropositive only to *B henselae*, 20.2% only to *B quintana*, and 39.5% to both *B henselae* and *B quintana*. In another study in North Carolina, 8.7% of cats were found to be seropositive only to *B henselae*, 7% only to *B quintana*, and 40.4% to both *B henselae* and *B quintana*.³³

In humans, *B quintana* infection typically results in a self-limiting febrile illness, with fever lasting up to 5 days, fatigue, conjunctival congestion, headache, myalgia, bone pain (particularly shin pain), rash, nystagmus, endocarditis, pericardial effusion, bacillary angiomatosis, and/or bacillary peliosis, particularly in individuals infected with human immunodeficiency viruses.^{4,23,26,34} *B quintana* and, rarely, *B henselae* can persist long-term if not treated properly in humans and are known causes of culture-negative endocarditis in humans.⁴

3

B bacilliformis

Humans are the only known reservoir of *B bacilliformis*, which is transmitted among humans via the bite of sand flies

(*Lutzomyia* spp) located in the Andes mountains, particularly in Peru, Colombia, and Ecuador.^{2,5,17,25,35,36}

B bacilliformis can cause Carrión's disease, a biphasic illness in humans that consists of acute and chronic phases. The acute phase (ie, Oroya fever) is characterized by a wide array of signs (eg, fever, chills, headache, intense myalgia, mental status changes, seizures, profound hemolytic anemia) and has a high fatality rate when untreated. The chronic phase (ie, verruga peruana [ie, Peruvian warts]) appears weeks to months after resolution of the acute phase and is characterized by angioproliferative skin lesions prone to ulceration and bleeding.^{4,35} Children and pregnant women may be particularly affected; complications can include fetal death, miscarriage, and/or premature birth.³⁵

An animal reservoir of *B Bacilliformis* has not been discovered but may still exist³⁵; there have been no documented cases of infection in dogs or cats.^{33,36,37}

4

B koehlerae

Cats are the primary reservoir of *B koehlerae* transmission to humans,^{3,5,6,24}

although *B koehlerae* and *B quintana* are less frequently isolated in cats as compared with *B henselae*.³ Evidence of *B koehlerae* infection has also been found in dogs and the fleas of wild gerbils (*Meriones libicus*).^{2,3,38} *C felis* (and possibly other flea species) is critical in the transmission of *B koehlerae* between animals and humans^{2,17}; however, additional arthropod vectors and other documented means of transmission of *Bartonella* spp are emerging.¹

There are an estimated 500 hospitalizations and 12 000 outpatient cases of cat scratch disease each year in the United States.⁸

CSD = cat scratch disease

OCCUPATIONAL HAZARD

For veterinary staff, *Bartonella* spp pose an occupational hazard.^{3,9,49} *B henselae* and *B vinsonii* subsp *berkhoffii* bacteremia have been documented in veterinarians and veterinary nurses who were exposed to arthropods, had frequent contact with cats and/or dogs, and/or experienced scratches or bites (primarily from cats).^{9,49} A serosurvey of US veterinarians and veterinary nurses found DNA from at least one *Bartonella* spp in 28% of subjects (*B henselae*, 56%; *B vinsonii* subsp *berkhoffii*, 26%; *B koehlerae*, 22%).²² Higher rates of headaches and irritability were reported in those found to be positive for *Bartonella* spp.²² A survey of 89 Spanish veterinarians found 73% of participants to be seropositive for at least one *Bartonella* spp; 11% were positive for *B quintana*, 56% for *B vinsonii* subsp *berkhoffii*, and 37% for *B henselae*.⁵⁰ Frequent exposure in the clinic is plausible because *Bartonella* spp has been isolated from blood, bodily fluids, effusions, and other biologic samples from cats, dogs, and humans.² Veterinary staff can reduce the risk for infection by practicing good hand hygiene (eg, wearing gloves, frequent handwashing) and by minimizing exposure to fleas and ticks, contact with arthropod feces and animal bites and scratches, and contact with bodily fluids from sick animals, cuts, and needle sticks.²

Routine ectoparasite control in pets can reduce risk for transmission of *Bartonella* spp to humans.^{2,5,24}

GLOBAL RELEVANCE

Bartonella spp have been found on every continent except Antarctica,³ and there is considerable belief that their cause of human illness has been significantly underdiagnosed.^{3,35,51,52} At least 17 species or subspecies of the 38 known *Bartonella* spp can cause disease in humans.³ More research is needed to learn about this organism and its epidemiology to manage its global impact.

Infection in cats can lead to subclinical infection and persistent bacteremia⁴ or, rarely, epithelioid hemangioendothelioma and systemic reactive angioendotheliomatosis.² *B koehlerae* infection in dogs has been associated with endocarditis and splenic disease.^{2,20,39,40} A serosurvey of dogs in North America identified a seropositivity rate of 2.4%.¹⁵

B koehlerae is an uncommon cause of illness in humans⁴ but has been associated with regional pain syndrome type I, hallucinations, sensory neuropathy, peripheral visual deficits, endocarditis, and other clinical conditions.²⁻⁵

5 *B vinsonii* subsp *berkhoffii*

Coyotes, dogs,⁴¹ and foxes are the main reservoirs of *B vinsonii* subsp *berkhoffii*,^{2,3} but the subspecies has also been found in cats, deer, horses, humans, a steer, and a red wolf.^{2,42,43} A serosurvey of dogs in the United States found a seropositivity rate of 1.5%¹⁴ and a higher rate of 3.6% in clinically ill dogs.⁴⁴ Signs in dogs may be subclinical or include anemia, arrhythmias, endocarditis, epistaxis, fever, hemangiosarcoma, myocarditis, splenomegaly, uveitis, and other signs; infection with this subspecies may also cause death.^{3,17,45,46}

B vinsonii subsp *berkhoffii* is rare in cats and humans. In cats, signs can include endocardial fibrosis complex, endomyocarditis, and osteomyelitis.^{3,42} Reported signs in humans include endocarditis and neurologic symptoms.^{2-4,23,47,48} Vectors for transmission include *C felis* and, possibly, ticks and *Pulex* spp fleas.² It is probable that *B koehlerae* and *B vinsonii* subsp *berkhoffii* are underrecognized, as testing for *Bartonella* spp other than *B bacilliformis*, *B quintana*, and *B henselae* is rarely performed.³

Conclusion

Although new species of *Bartonella* are discovered frequently, the most widespread and well-described in humans and animals is *B henselae*. Many *Bartonella* spp can produce similar clinical signs in a host, but these infections can be subclinical and chronic. Vectors play a significant role in the

epidemiology of all *Bartonella* spp; transmission by other routes, particularly bites and scratches, makes *Bartonella* spp an occupational risk to those working closely with animals, especially those with a flea infestation. The occupational risks for

Bartonella spp infection in veterinary staff can be reduced through a better understanding of *Bartonella* spp and by adhering to good prevention measures when working with animals (see **Occupational Hazard**). ■■■

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Heartgard® Plus

(ivermectin/pyrantel)

CHEWABLES

CAUTION: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

INDICATIONS: For use in dogs to prevent canine heartworm disease by eliminating the tissue stage of heartworm larvae (*Dirofilaria immitis*) for a month (30 days) after infection and for the treatment and control of ascarids (*Toxocara canis*, *Toxascaris leonina*) and hookworms (*Ancylostoma caninum*, *Uncinaria stenocephala*, *Ancylostoma braziliense*).

DOSAGE: HEARTGARD® Plus (ivermectin/pyrantel) should be administered orally at monthly intervals at the recommended minimum dose level of 6 mcg of ivermectin per kilogram (2.72 mcg/lb) and 5 mg of pyrantel (as pamoate salt) per kg (2.27 mg/lb) of body weight. The recommended dosing schedule for prevention of canine heartworm disease and for the treatment and control of ascarids and hookworms is as follows:

Dog Weight	Cheewables Per Month	Ivermectin Content	Pyrantel Content	Color Coding On Foil Backing and Carton
Up to 25 lb	1	68 mcg	57 mg	Blue
26 to 50 lb	1	136 mcg	114 mg	Green
51 to 100 lb	1	272 mcg	227 mg	Brown

HEARTGARD Plus is recommended for dogs 6 weeks of age and older.

For dogs over 100 lb use the appropriate combination of these chewables.

ADMINISTRATION: Remove only one chewable at a time from the foil-backed blister card. Return the card with the remaining chewables to its box to protect the product from light. Because most dogs find HEARTGARD Plus palatable, the product can be offered to the dog by hand. Alternatively, it may be added intact to a small amount of dog food. The chewable should be administered in a manner that encourages the dog to chew, rather than to swallow without chewing. Chewables may be broken into pieces and fed to dogs that normally swallow treats whole.

Care should be taken that the dog consumes the complete dose, and treated animals should be observed for a few minutes after administration to ensure that part of the dose is not lost or rejected. If it is suspected that any of the dose has been lost, redosing is recommended.

HEARTGARD Plus should be given at monthly intervals during the period of the year when mosquitoes (vectors), potentially carrying infective heartworm larvae, are active. The initial dose must be given within a month (30 days) after the dog's first exposure to mosquitoes. The final dose must be given within a month (30 days) after the dog's last exposure to mosquitoes.

When replacing another heartworm preventive product in a heartworm disease preventive program, the first dose of HEARTGARD Plus must be given within a month (30 days) of the last dose of the former medication.

If the interval between doses exceeds a month (30 days), the efficacy of ivermectin can be reduced. Therefore, for optimal performance, the chewable must be given once a month on or about the same day of the month. If treatment is delayed, whether by a few days or many, immediate treatment with HEARTGARD Plus and resumption of the recommended dosing regimen will minimize the opportunity for the development of adult heartworms.

Monthly treatment with HEARTGARD Plus also provides effective treatment and control of ascarids (*T. canis*, *T. leonina*) and hookworms (*A. caninum*, *U. stenocephala*, *A. braziliense*). Clients should be advised of measures to be taken to prevent reinfection with intestinal parasites.

EFFICACY: HEARTGARD Plus Chewables, given orally using the recommended dose and regimen, are effective against the tissue larval stage of *D. immitis* for a month (30 days) after infection and, as a result, prevent the development of the adult stage. HEARTGARD Plus Chewables are also effective against canine ascarids (*T. canis*, *T. leonina*) and hookworms (*A. caninum*, *U. stenocephala*, *A. braziliense*).

ACCEPTABILITY: In acceptability and field trials, HEARTGARD Plus was shown to be an acceptable oral dosage form that was consumed at first offering by the majority of dogs.

PRECAUTIONS: All dogs should be tested for existing heartworm infection before starting treatment with HEARTGARD Plus which is not effective against adult *D. immitis*. Infected dogs must be treated to remove adult heartworms and microfilariae before initiating a program with HEARTGARD Plus.

While some microfilariae may be killed by the ivermectin in HEARTGARD Plus at the recommended dose level, HEARTGARD Plus is not effective for microfilariae clearance. A mild hypersensitivity-type reaction, presumably due to dead or dying microfilariae and particularly involving a transient diarrhea, has been observed in clinical trials with ivermectin alone after treatment of some dogs that have circulating microfilariae.

Keep this and all drugs out of the reach of children.

In case of ingestion by humans, clients should be advised to contact a physician immediately. Physicians may contact a Poison Control Center for advice concerning cases of ingestion by humans.

Store between 68°F - 77°F (20°C - 25°C). Excursions between 59°F - 86°F (15°C - 30°C) are permitted. Protect product from light.

ADVERSE REACTIONS: In clinical field trials with HEARTGARD Plus, vomiting or diarrhea within 24 hours of dosing was rarely observed (1.1% of administered doses). The following adverse reactions have been reported following the use of HEARTGARD: Depression/lethargy, vomiting, anorexia, diarrhea, mydriasis, ataxia, staggering, convulsions and hypersalivation.

SAFETY: HEARTGARD Plus has been shown to be bioequivalent to HEARTGARD, with respect to the bioavailability of ivermectin. The dose regimens of HEARTGARD Plus and HEARTGARD are the same with regard to ivermectin (6 mcg/kg). Studies with ivermectin indicate that certain dogs of the Collie breed are more sensitive to the effects of ivermectin administered at elevated dose levels (more than 16 times the target use level) than dogs of other breeds. At elevated doses, sensitive dogs showed adverse reactions which included mydriasis, depression, ataxia, tremors, drooling, paresis, recumbency, excitability, stupor, coma and death. HEARTGARD demonstrated no signs of toxicity at 10 times the recommended dose (60 mcg/kg) in sensitive Collies. Results of these trials and bioequivalency studies, support the safety of HEARTGARD products in dogs, including Collies, when used as recommended.

HEARTGARD Plus has shown a wide margin of safety at the recommended dose level in dogs, including pregnant or breeding bitches, stud dogs and puppies aged 6 or more weeks. In clinical trials, many commonly used flea collars, dips, shampoos, anthelmintics, antibiotics, vaccines and steroid preparations have been administered with HEARTGARD Plus in a heartworm disease prevention program.

In one trial, where some pups had parvovirus, there was a marginal reduction in efficacy against intestinal nematodes, possibly due to a change in intestinal transit time.

HOW SUPPLIED: HEARTGARD Plus is available in three dosage strengths (See DOSAGE section) for dogs of different weights. Each strength comes in convenient cartons of 6 and 12 chewables.

For customer service, please contact Merial at 1-888-637-4251.

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