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Bartonellosis, One Health and all creatures great and small

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Background – Bartonellosis is a zoonotic infectious disease of worldwide distribution, caused by an expanding number of recently discovered *Bartonella* spp.

Objectives – This review serves as an update on comparative medical aspects of this disease, including the epidemiology, pathogenesis, clinical diagnosis, treatment and challenges.

Results – Of comparative medical importance, *Bartonella* spp. are transmitted by several arthropod vectors, including fleas, keds, lice, sand flies, ticks and, potentially, mites and spiders. Prior to 1990, there was only one named *Bartonella* species (*B. bacilliformis*), whereas there are now over 36, of which 17 have been associated with an expanding spectrum of animal and human diseases. Recent advances in diagnostic techniques have facilitated documentation of chronic bloodstream and dermatological infections with *Bartonella* spp. in healthy and sick animals, in human blood donors, and in immunocompetent and immunocompromised human patients. The field of *Bartonella* research remains in its infancy and is rich in questions, for which patient relevant answers are badly needed. Directed *Bartonella* research could substantially reduce a spectrum of chronic and debilitating animal and human diseases, and thereby reduce suffering throughout the world.

Conclusion – A One Health approach to this emerging infectious disease is clearly needed to define disease manifestations, to establish the comparative infectious disease pathogenesis of this stealth pathogen, to validate effective treatment regimens and to prevent zoonotic disease transmission.

Preface

James Herriot published "All Creatures Great and Small" in 1972, 2 years before I graduated from the University of Georgia, College of Veterinary Medicine with the degree Doctor of Veterinary Medicine. Herriot embodied the "One Health Philosophy" by providing the best medical care possible to all creatures, regardless of their size, disposition, societal stature or economic worth. As a veterinarian, Herriot was very familiar with zoonotic diseases, such as brucellosis, rabies, tuberculosis, toxoplasmosis and others that were prevalent at the time. He also understood the critical role of genetics, nutrition and environmental toxins (naturally occurring and man-made), as mediators of infectious and noninfectious disease expression. Importantly, it would be another 20 years before Herriot, I and most other health care providers would come to know of the existence of the genus *Bartonella.*

Currently, resurgent efforts by groups around the world are promoting the importance of the "One Health Philosophy", which involves coordinated interaction among animal, human and environmental health professionals. I am sure that James Herriot would applaud these efforts and revel in the contemporary success stories. As one example, recently the World Organisation for Animal Health (see http://www.oie.int/) in conjunction with the World Small Animal Veterinary Association issued a One Health proclamation to eliminate rabies, which claims the lives of nearly 60,000 people each year throughout the world. On 3 November 2016, the first Global One Health Day was celebrated, emphasizing the connection between the health of animals, people and the environment.

Introduction

The genus *Bartonella* and the disease bartonellosis represent one of the more important contemporary One Health challenges of modern times. Bartonellosis also offers an opportunity to demonstrate the societal benefits of a One Health Approach to disease prevention in general and to enhance the comparative medical understanding of this emerging infectious disease.

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Coordinated efforts are needed to clarify the medical importance of *Bartonella* spp. (currently 36 named and 17 Candidatus species) as a cause of disease in animals and humans. This review will focus on the complex interplay between bartonellosis, One Health, and all creatures great and small.

Bartonella species are fastidious Gram-negative bacteria that are highly adapted to a mammalian reservoir host within which the bacteria usually cause a long lasting intra-erythrocytic bacteraemia and endotheliotropic infection, often not in association with concurrent disease.[1–3] These facts are of particular importance to veterinarians, physicians and other healthcare professionals, because an increasing number of animal reservoir hosts have been identified for various *Bartonella* species (Table 1). Among numerous other examples, *Bartonella henselae* has co-evolved with cats, *Bartonella vinsonii* subsp. *berkhoffii* and *Bartonella rochalimae* have co-evolved with wild canines, *Candidatus Bartonella melophagi* has co-evolved with sheep, and *Bartonella bovis* has co-evolved with cattle. Importantly, as new *Bartonella* spp. are discovered, the list of reservoir-adapted *Bartonella* species, including a large number of rodent and bat species, continues to grow exponentially.[2,3] Coevolution has created a hidden, large and constant source of infection for accidental hosts in natural environments.[4–6]

In the natural reservoir host, chronic bacteraemia with a *Bartonella* species can frequently be detected by blood culture or PCR in outwardly healthy animals.[2,3] Infection with *B. henselae* and *Bartonella clarridgeiae,* species associated with cats and their fleas, has been reported in healthy Brazilian blood donors, suggesting that asymptomatic infection occurs in humans as well as cats, dogs and other animals.[5,7] In contrast to the reservoir-adapted host, the microbiological detection of a *Bartonella* spp. in a nonreservoir adapted host can be extremely difficult.[8–11] Most, although not all, diseases caused by *Bartonella* spp. occur in accidental hosts and these organisms are being

Table 1. *Bartonella* species or subspecies, primary reservoir hosts, confirmed or potential vectors, and infection in accidental hosts. Details are provided in references 2, 3, 15 and 49.

Bartonella species	Main reservoir	Potential vectors	Accidental hosts
B. acomydis	Mice (Acomys russatus)	Unknown	
B. alsatica	Rabbits (*Oryctolagus cuniculus*)	Fleas, ticks	Humans
Candidatus B. antechini	Yellow-footed antechinus (*Antechinus flavipes)*	Fleas, ticks	
B. bacilliformis	Humans	Fleas, sandflies	
B. birtlesii	Wood mice (*Apodemus* spp.)	Fleas	
B. bovis (weissii)	Domestic cattle (*Bos taurus*)	Biting flies, ticks	Cats, Dogs Humans,
B. callosciuri	Squirrel (Callosciurus notatus)	Unknown	
B. capreoli	Roe deer (*Capreolus capreolus*)	Biting flies, ticks	
B. chomelii	Domestic cattle (*Bos taurus*)	Biting flies, ticks	
B. clarridgeiae	Cats (*Felis catus*)	Fleas, ticks	Humans, Dogs
B. doshiae	Meadow voles (*Microtus agrestis*), Rats (*Rattus* spp)	Fleas	Humans
B. elizabethae	Rats (*Rattus norvegicus*)	Fleas	Humans, Dogs
B. florenciae	Shrew (*Crocidura russula*)	Unknown	
B. grahamii	Voles (*Clethrionomys* spp.), mice (*Apodemus* spp)	Fleas	Humans
B. henselae	Cats (*Felis catus*), dogs (*Canis familiaris)*	Fleas, ticks	Humans, Dogs
B. japonica	Mice (*Apodemus argenteus*)	Lice (*Hoplopura affinis)*	
B. koehlerae	Cats (*Felis catus*), gerbils (*Meriones lybicus*)	Fleas	Humans
B. mayotimonesis	Daubenton's bat (*Myotis daubentonii*)	Bat flies, fleas	Humans
*B. melophagi**	Sheep (*Ovis* spp.)	Sheep keds	Humans
Candidatus B. merieuxii	Dogs (*Canis familiaris*)	Fleas	
B. pachyuromydis	Mice (Pachyuromys duprasi)		
B. peromysci	Field mice (*Peromyscus* spp.)	Fleas	
B. queenslandensis	Rats (*Rattus* spp)	Fleas	
B. quintana	Humans, gerbils (*Meriones lybicus*)	Human body lice, fleas	Cats, Dogs
"B. rattimassiliensis"	Rats (*Rattus* spp)	Fleas	
B. rattaustraliani	Rats (*Rattus* spp)	Fleas	
"B. rochlimaea"	Dogs (*Canis familiaris*)	Sandflies	Humans
B. schoenbuchensis	Roe deer (*Capreolus capreolus*)	Deer keds, biting flies, ticks	Humans
B. senegalensis	Burrowing rodents	Soft tick *Ornithodoros sonrai*	
B. silvatica	Mice (*Apodemus speciosus*)		
B. talpae	Moles (*Talpa europaea*)	Fleas	
"B. tamiae"	Rat (*Rattus* spp.)	Fleas	Humans
B. taylorii	Mice (*Apodemus* spp.), gerbils (Meriones lybicus), voles (*Clethrionomys* spp.)	Fleas	
B. tribocorum	Rats (*Rattus* spp), mice (*Apodemus* spp.)	Fleas	
B. vinsonii subsp. *arupensis*	White-footed mice (*Peromyscus leucopus*)	Fleas, ticks	Humans
B. vinsonii subsp. *berkhoffii*	Coyotes (*Canis latrans*), dogs (*Canis familiaris*), foxes (*Urocyon* spp.*)*	Ticks	Humans
B. vinsonii subsp. *vinsonii*	Meadow voles (*Microtus pennsylvanicus*)	Ear mites	
"B. volans"	Southern flying squirrels (*Glaucomys volans*)	Fleas	Humans
"B. washoensis"	California ground squirrel (*Spermophilus beecheyi*), rabbits (*Oryctolagus cuniculus*)	Fleas, ticks	Humans, Dogs

increasingly implicated as a cause of zoonotic infections.[8–11] Mechanisms that facilitate persistent *Bartonella* bacteraemia in mammals remain incompletely understood. Intra-endothelial and intra-erythrocytic location of these bacteria represents a unique strategy for bacterial persistence.[2,6] Nonhaemolytic intracellular colonization of erythrocytes and invasion of endothelial cells preserves these organisms for efficient vector transmission, facilitates movement throughout the vascular system, protects *Bartonella* from the host immune response and potentially contributes to diminished antimicrobial efficacy. In addition to erythrocytic and endotheliotropic cell invasion, *in vitro* studies indicate that *Bartonella* spp. can infect dendritic cells, microglial cells, pericytes, monocytes and CD34 + bone marrow progenitor cells.[6] Thus in the context of disease pathogenesis, these bacteria can infect numerous cell types, can access any location within the body via small blood vessels and, potentially, through lymphatics (which has not been studied to date), can promote endothelial cell proliferation and can slow endothelial cell death by inhibition of apoptotic pathways. These and other factors make *Bartonella* the perfect stealth pathogen, defined as an organism that can induce persistent infection in association with immune evasion and fluctuating symptoms varying in type and severity.[2,3,6]

One Health and the medical aspects of *Bartonella e*pidemiology

As a genus, *Bartonella* epidemiology continues to evolve and change as reflected in trends between earlier and more recent reviews.[1–3,12–15] *Bartonella henselae, B. vinsonii* subsp. *berkhoffii* and *Bartonella koehlerae* appear to be the most medically important species to infect cats, dogs, horses and potentially humans. Other *Bartonella* spp. have been less frequently reported in association with various disease processes in animals and humans (Table 1). *Bartonella bacilliformis* and *Bartonella quintana* are also important human pathogens, for which primates are considered the reservoir hosts.[12–14] As an important example of an evolution in ecological understanding, *B. henselae* was initially isolated from a HIV-infected human and subsequently from cats around the world.[1–3] Subsequently, *B. henselae* bacteraemia has been documented in cows, dogs, horses, marine mammals, small terrestrial mammals and sea turtles, making the epidemiology of this single medically important species much more complex than initially anticipated.[3,15]

In contrast to the initial *B. henselae* isolation from an immunocompromised human, *B. vinsonii* subsp. *berkhoffii* was initially isolated from a dog with endocarditis. Subsequently this subspecies has been isolated or DNA PCR-amplified from cats, coyotes, deer, fox, horses and human patients.[12,15] As described below, successful microbiological isolation of *Bartonella* species is difficult. Long-term administration of immunosuppressive corticosteroids for a presumptive diagnosis of systemic lupus erythematosus with cutaneous vasculitis may have facilitated the isolation of this original type strain of *B. vinsonii* subsp. *berkhoffii* (the first *Bartonella* sp. reported to infect a dog). Immunosuppression may also have contributed to the location of these bacteria on the aortic and mitral valves resulting in vegetative valvular endocarditis, as has been reported in immunosuppressed human patients.[3,15] *Bartonella vinsonii* subsp. *berkhoffii* seroprevalence in 1,920 sick dogs from North Carolina (NC) or surrounding states in the United States was evaluated at a tertiary care veterinary teaching hospital.[16] Using a reciprocal titre of >32, 3.6% of sick dogs were *B. vinsonii* subsp. *berkhoffii* seroreactive. Risk factors associated with seroreactivity included: heavy tick exposure [Odds ratio (OR) 14.2], cattle exposure (OR 9.3), a rural versus urban environment (OR 7.1) and heavy flea exposure (OR 5.6). These data supported the hypothesis that exposure to *B. vinsonii* subsp. *berkhoffii* was more likely to occur in dogs in rural environments that had arthropod infestations and were allowed to roam freely.

In support of the potential for tick transmission of *B. vinsonii* subsp. *berkhoffii*, 36% of serum samples derived from dogs naturally infected with *Ehrlichia canis* were seroreactive to *B. vinsonii* subsp. *berkhoffii* antigens.[16,17] In contrast, sera from dogs experimentally infected with *Rickettsia rickettsii* or *E. canis*, two closely related alpha proteobacteria species, were not cross-reactive to *Bartonella* antigens. As *E. canis* is thought to be transmitted solely by *Rhipicephalus sanguineous*, natural transmission of *B. vinsonii* subsp. *berkhoffii* by this tick was suspected. As reviewed previously, the possibility of tick transmission was further supported by additional studies involving *Ehrlichia* spp. co-exposures from the same geographical region (NC), in which seroreactivity to *E. canis* and *B. vinsonii* subsp. *berkhoffii* antigens was 30% and 89%, respectively.[3] Similarly, *B. vinsonii* subsp. *berkhoffii* seroprevalence was 10% (four of 40 dogs) in dogs with suspected tick-borne illness from Israel, 36% in dogs with fever and thrombocytopenia from Thailand, and 6.6% of stray and rural dogs in Turkey.[3]

Further studies from around the world have emphasized co-exposures and co-infections with vector-borne organisms (particularly fleas and ticks) in pets and people. As one example involving dogs, a vector-borne disease surveillance study that spanned 2004–2010, (N = 14,496 serum samples) submitted to the North Carolina State University, College of Veterinary Medicine, Vector Borne Disease Diagnostic Laboratory for diagnostic purposes were tested using immunofluorescent antibody (IFA) and enzyme linked immunosorbent assay (ELISA) assays. Seroreactivity to *R. rickettsii*, *Borrelia burgdorferi, Ehrlichia* spp., *B. henselae*, *Anaplasma* spp., *B. vinsonii* subsp. *berkhoffii*, *Babesia canis* and *Dirofilaria immitis* was 10.4%, 5.2%, 4.3%, 3.8%, 1.9%, 1.5%, 1.1% and 0.8%, respectively.[18] In contrast, a study from Algeria involving stray and pet dogs, the *Anaplasma* spp., *Borrelia* spp., *E. canis, B. henselae* and *B. vinsonii* subsp. *berkhoffii* seroprevalences were 47.7%. 37.6%, 30.0%, 32.4% and 27%, respectively.[19] Although seroepidemiological data continue to support tick transmission of *B. vinsonii* subsp. *berkhoffii* and potentially other *Bartonella* spp. to dogs, the mode of transmission has not been proven for this subspecies. Importantly, evolving evidence supports the possibility that *Ixodes* spp. are transmitting *B. henselae,* in addition to *Borrelia, Anaplasma* and *Babesia* spp. to animals and humans throughout the Northern hemisphere.[20]

Studies from Hawaii, USA, UK and Japan were among the first to document *B. henselae* seroprevalences of 6.5% (two of 31), 3.0% (three of 100) and 7.7% (four of 52) in dogs, respectively.[1,3] In the context of clinical diagnosis, *B. henselae* is the most common *Bartonella* species found in the blood of sick dogs using the *Bartonella alpha-Proteobacteria* growth medium (BAPGM) enrichment blood culture platform; however, most sick bacteraemia dogs, despite a history of chronic illness, do not have detectable *B. henselae* antibodies by immunofluorescent antibody testing, for reasons that remain unclear.[21] As discussed under the diagnosis section, seronegative bacteraemia may result in a substantial underestimation of *Bartonella* seroprevalence in animal and human studies.

In cats, *B. henselae, B. clarridgeiae* and *B. koehlerae* DNA have been amplified or the organisms have been isolated most frequently from clinically healthy cats that have experienced flea infestations.[1–3] Flea-associated transmission of *B. henselae* by *Ctenocephalides felis* amongst cats has been documented in laboratory studies.[22] In a laboratory transmission study, *C. felis* also transmitted *B. henselae* to dogs (Lappin M and Breitschwerdt E, unpublished data). Clinical, epidemiological and laboratory studies support the transmission of *B. koehlerae, B. clarridgeiae, B. quintana* and potentially *B. vinsonii* subsp. *berkhoffii* by *C. felis*, and potentially other flea species such as *Pulex* spp.[23–26] Although the source of feline infection was not determined, a feral cat transmitted *B. quintana* to a human by scratch or bite. Subsequently, the feral cat was shown to be *B. quintana* bacteraemic.[27] Historically, *B. quintana,* the cause of Trench Fever in World War I and more recently Urban Trench Fever throughout the world, was thought to be transmitted solely by the human body louse (*Pediculus humanus*) and humans were considered the sole reservoir hosts. It now appears that cats can be a reservoir host and that fleas may be the source of infection for cats and potentially humans.[25,27] As described above for *B. henselae* and *B. vinsonii* subsp. *berkhoffii,* epidemiological understanding of *B. quintana* continues to change in complexity as additional potential vectors and reservoir hosts are identified.

In flea endemic areas, *Bartonella* spp. seroprevalence rates in cats can be greater than 90% and bacteraemia rates can be greater than 50%.[1–3] In a study from the United States involving PCR of blood from feral cats and raccoons, the prevalence of *Bartonella* bacteraemia was nearly identical, 48% in cats and 43% in raccoons.[28] Also, rat mite (*Ornithonyssus bacoti*) transmission of *B. henselae* to a woman and her pet dogs was implicated after removal of raccoons from under a house in New York, USA.[29] Thus, cats (both pet and feral), raccoons, mongoose and potentially other animals can serve as a source of *B. henselae* infection for humans and other animals, such as pet dogs. In addition to fleas, ticks, mites and spiders may also contribute to the transmission of *B. henselae*.

Fleas and flea infestations in households and on pets are of increasing zoonotic and medical importance to dermatologists, parasitologists, physicians, veterinarians and other health professionals. Collectively, recent studies emphasize an underappreciated role for mammals other than cats as reservoir hosts, for vectors other than fleas, lice and sandflies as a source of transmission, and for potential *C. felis* (and potentially other flea species) to be vector competent for the transmission of several *Bartonella* spp. to cats, dogs and humans. It is increasingly clear that the ecology and epidemiology of bartonellosis in many environmental settings is much more complex and dynamic due to the large number of *Bartonella* species, the large number of reservoir hosts and vectors, and the numerous modes of transmission, than was appreciated a decade ago.[30]

Pathogenesis and pathology

Despite substantial efforts by researchers around the world, relevant animal models to study disease pathogenesis have not been forthcoming. Because *Bartonella* spp. can cause chronic intra-erythrocytic and endotheliotropic infections in cats, dogs, humans and numerous other animal species that can span weeks, months or potentially years in duration, characterizing the pathogenesis of naturally occurring disease remains challenging.[1–3,15] Similar to other highly adapted intracellular vector-transmitted pathogens, the factors that ultimately result in disease manifestations are yet to be determined, but are most likely multifactorial and include virulence differences among *Bartonella* species and strains, differences in the host immune response and other epiphenomena such as co-infection, immunosuppression, concurrent noninfectious diseases and malnutrition.

Because bartonellosis is characterized by persistent intravascular infection, subsets of animal and human patients develop endocarditis, myocarditis or various forms of vascular pathology (Table 2). In addition, persistent infection may predispose to autoimmune (e.g. immune-mediated anaemia or immune-mediated thrombocytopenia) and immune-mediated (leukocytoclastic vasculitis or immune complex glomerulonephritis) manifestations as a component of the disease pathogenesis.[3,15] Similar to what is known for babesiosis, a tick-borne intra-erythrocytic pathogen, stress, hard work, parturition, concurrent or sequential infection with other vector-borne organisms or therapeutic immunosuppression may contribute to the development of pathology in an individual who was previously in a state of premunition (term denoting "infection immunity" and reflecting an immunological balance between the infectious agent and the host immune response) with the bacteria.

Although minimally studied to date, persistent infection with a *Bartonella* spp. in a sick individual may ultimately result in organism-induced immunosuppression. Experimental inoculation of dogs with culture-grown *B. vinsonii* subsp. *berkhoffii* resulted in impaired phagocytosis by monocytes, sustained suppression of peripheral blood CD8 + lymphocytes accompanied by an altered cell surface phenotype, an increase in CD4 + lymphocytes in the peripheral lymph nodes and potentially impaired B cell antigen presentation.[31] Thus, bacteria-induced immunosuppression could predispose dogs to secondary infections, further contributing to the wide array of clinical manifestations that occur in naturally infected dogs. Cats

Table 2. *Bartonella*-associated endocarditis, myocarditis and vascular pathology. Details are provided in references 12–15.

	Host(s)
Verruga peruana	
B. bacilliformis	Human
Candidatus B. ancashi	Human
Bacillary angiomatosis	
B. henselae	Human
B. quintana	Human
B. vinsonii subsp. *berkhoffii*	Dog
Bacillary peliosis	
B. henselae	Dog, human
Endocarditis	
B. alsatica	Human
B. bacilliformis	Sea otter*
B. bovis	Cattle
B. clarridgeiae	Dog
B. elizabethae	Human
B. henselae	Human, cat, dog, coyote,* sea otter*
B. koehlerae	Human, dog
B. quintana	Human, dog
B. rochalimae	Dog, coyote*
B. vinsonii subsp. *arupensis*	Human
B. vinsonii subsp. *berkhoffii*	Human, dog, coyote*
B. washoensis	Human, dog
Candidatus B. mayotimonensis	Human
Bartonella spp. JM-1	Sea otter*
Myocarditis	
B. henselae	Human, cat
B. vinsonii subsp. *vinsonii*	Dog
B. washoensis	Human
Aneurysm	
B. henselae	Human
B. quintana	Human
Vasculitis and/or thrombosis	
B. henselae	Human, dog
B. quintana	Human
Haemangiosarcoma	
B. vinsonii subsp. *berkhoffii*	Dog
Haemangiopericytoma	
B. henselae	Dog, horse
B. vinsonii subsp. *berkhoffii*	Dog, horse, red wolf
Epithelioid haemangioendothelioma	
B. vinsonii subsp. *berkhoffii*	Human
B. henselae	Human
B. koehlerae	Human
Systemic reactive angioendotheliomatosis	
B. henselae	Cat, cattle
B. koehlerae	Cat
B. vinsonii subsp. *vinsonii*	Cat

* *Bartonella* DNA was amplified from nondiseased mitral and aortic valves of coyotes and sea otters.

infected with *Bartonella* spp. are commonly co-infected with haemoplasmas and at times, more than one *Bartonella* sp.[3] However, whether co-infections magnify disease manifestations in cats is unclear, and in most epidemiological studies co-infection with a haemotropic *Mycoplasma* sp., feline immunodeficiency virus (FIV) and *Bartonella* did not appear to potentiate illness.[1,3] In the context of comparative medicine and a One Health approach to bartonellosis, co-infections with haemotropic *Mycoplasma* spp. and *B. henselae* have been recently reported in humans.[32]

The microbiological and molecular pathogenesis of *Bartonella*-induced vasoproliferative lesions have been studied in detail and readers are referred to reviews.[6,14,33] Although persistent bacteraemia most likely plays a role, the cellular and immunopathogenesis of other *Bartonella*-associated pathological lesions, including endocarditis, myocarditis, vasculitis and granulomatous tissue inflammation (lymphadenitis, hepatitis, panniculitis, splenitis) has not been studied to any extent.

Reviews have emphasized an emerging role for a dermal niche, as well as the previously described vascular niche, as an important pathogenic component of the pathophysiology of *Bartonella* infections.[6] Once transmitted to the host by inoculation of contaminated arthropod faeces (fleas, mites and lice) or potentially by a bite (tick or sandfly), the bacterium penetrates the dermal barrier, most often in conjunction with scratching or through a pre-existing abrasion. Subsequently, *Bartonella* are thought to infect dermal dendritic cells, which then transport (macrophages serving as a Trojan horse) bacteria to the endothelium to create a vascular niche. The endothelial or vascular niche provides the bacterium with a means of seeding the blood with organisms on a sporadic basis, resulting in infection of CD34 + cells in the bone marrow, as well as circulating erythrocytes and monocytes. The clinical relevance of the dermal niche for human dermatologists and other clinicians is only just now being considered on a research basis. Previous comparative infectious disease observations suggest that the dermal niche may be involved in panniculitis, cutaneous vasculitis and cutaneous vasoproliferative lesions such as bacillary angiomatosis, across animal species.[34–37]

In the context of comparative medicine, *B. henselae* has been reported in dogs and humans with granulomatous lymphadenopathy, granulomatous hepatitis and fever of unknown origin; it appeared to cause steatitis and prostatitis in a dog following flea transmission.[14,38,39] It is also possible that a subset of striae lesions, particularly in children, are caused by *Bartonella* spp. infections.[9] *Bartonella henselae* DNA was amplified from four of 29 (13.8%) paraffin-embedded canine histiocytoma tissues; however, the prevalence did not vary statistically from the control group.[40] Subsequent investigations have determined that bacteria DNA is rapidly degraded in formalin-fixed paraffin embedded skin (J.S. Pendergraft, N. Balakrishnan, E.B. Breitschwerdt, unpublished data), a factor that may have influenced the histiocytoma study conclusions. Thus, frozen, rather than formalin-fixed, paraffin-embedded dermal biopsy tissue would be recommended for diagnostic and investigational purposes when attempting to determine the presence or absence of *Bartonella* species DNA. Because aseptic measures to completely remove rapid-growing dermal bacteria such as *Staphylococcus* and *Corynebacteria,* are unlikely to be effective, using an enrichment skin culture approach as described below for blood and other aseptically obtained effusion or tissue samples is unlikely to be successful. For human and veterinary clinicians, determining if the dermal niche of *Bartonella* spp. is involved in the pathogenesis of striae in children, panniculitis or "flea allergy dermatitis" in dogs, may represent relevant research questions. Also in the context of dermatology, *Bartonella* DNA was amplified from house dust mites, a known cause of cutaneous allergic reactions.[41,42]

The spectrum of disease manifestations in animals and humans with serological, culture or PCR evidence of bartonellosis varies substantially. Reasons for variations in symptomatology as well as the varied pathology most likely relate to differences in organism virulence, which has now been documented for *B. henselae* strains, variation in the genetically mediated host immune response following infection, the duration of infection, inadequate or excessive nutrition, co-infection with other bacterial, viral or protozoal organisms, and noninfectious co-morbidities. In addition to complicating diagnostic confirmation of *Bartonella* spp. infections, these factors also complicate efforts to prove disease causation. From an evolutionary perspective, it is obvious that vectors, vector-borne organisms, and animal and human hosts have developed a highly adapted form of interaction over millions of years of coexistence. In general, vectors need blood for nutrition; some bacterial, rickettsial, protozoal and viral organisms need an intracellular environment to survive and, immunologically, many animal hosts appear to be able to support chronic infection with one or more vector-borne organisms for months to years without obvious deleterious effects. These factors serve to illustrate the potential difficulty in establishing disease causation in cats, dogs or people infected with a *Bartonella* spp. or when co-infected with multiple vector-borne pathogens.

We have proposed an addition to Koch's postulates entitled the Postulate of Comparative Infectious Disease Causation.[14] In satisfying this postulate we have stated that: "causation can be established if the same infectious agent (or combination of agents) are isolated or organism specific DNA sequences are amplified from a naturally occurring pathological entity found in at least three different mammalian genera". Based upon this postulate, *Bartonella* spp. appear to be able to cause endocarditis, granulomatous inflammatory diseases, particularly involving the heart, liver, lymph nodes and spleen, persistent intravascular infections, and the induction of vasoproliferative tumours. In the context of comparative infectious disease causation, *B. henselae* was amplified and sequenced from the liver of a dog with peliosis hepatitis, a unique pathological lesion initially reported in *B. henselae* infected HIV patients and from another dog with granulomatous hepatitis, a histopathological lesion reported with some frequency in *B. henselae*-infected children and adults.[3,14] *Bartonella clarridgeiae* DNA was amplified and sequenced from the liver of a Doberman dog with copper storage disease and from the aortic valve of a dog with vegetative valvular endocarditis.[2,3] *Bartonella elizabethae*, a species that infects rodents, was found in a dog that had shown chronic weight loss culminating in sudden unexplained death and from a human endocarditis patient.[2,3] Based upon a large seroepidemiological, controlled study from the University of California (Davis), dogs that were seroreactive to either *B. henselae, B. clarridgeiae* or *B. vinsonii* subsp. *berkhoffii* were referred for evaluation of lameness, neutrophilic polyarthritis, nasal discharge, epistaxis or splenomegaly.[13] *Bartonella henselae* and *B. vinsonii* subsp. *berkhoffii* were isolated from the synovial fluid of a dog with polyarthritis[43] and from the blood of dogs with epistaxis.[44] Based upon clinical observations, it seems likely that the spleen plays an important immunomodulatory role in controlling persistent *Bartonella* spp. bacteraemia in animals and people, as occurs with other intra-erythrocytic infections.[11,35] The extent to which *Bartonella* spp. induce splenic pathology in animals and humans deserves additional research consideration.[11,45]

Clinical findings

The complete spectrum of disease associated with *Bartonella* infection in cats, dogs, humans and most other animal species is currently unknown. Endocarditis, has been reported in cats, cows, dogs and humans, infected with a spectrum of reservoir-adapted *Bartonella* spp (Table 2).[2] In dogs, intermittent lameness, bone pain, epistasis or fever of unknown origin have preceded the diagnosis of endocarditis by several months, whereas other dogs will present with an acute history of cardiopulmonary decompensation (ARDS or acute respiratory distress syndrome) without a history of premonitory signs. Cardiac arrhythmias secondary to myocarditis can be detected in cats and dogs without echocardiographic evidence of endocarditis.[46] Granulomatous lymphadenitis has been associated with *B. vinsonii* subsp. *berkhoffii* and *B. henselae* in dogs.[14,38] In dogs, *Bartonella* species appear to contribute to the development of dermatological lesions indicative of a cutaneous vasculitis, panniculitis, as well as anterior uveitis, polyarthritis, meningoencephalitis and immune-mediated haemolytic anaemia.[3,13,47] Additional research efforts, using carefully designed case-controlled studies, are necessary to establish the frequency and extent to which *Bartonella* spp. contribute to dermatological, ocular, orthopaedic, neurological or haematological abnormalities in dogs (and humans).

Clinically, many disease manifestations also have been attributed to *Bartonella* spp. infections in cats.[1–3] However, it is very difficult to prove disease associations in cats in the field because of the high prevalence rates in nonclinical carriers. In research cats that are infected by exposure to *C. felis*, fever, endocarditis and myocarditis are the most common disease manifestations.[1,3,46,48] As discussed for dogs, additional case-controlled, prospective studies are needed in cats.[48]

Due to the spectrum of clinical and pathological abnormalities that have been associated with *Bartonella* spp. infections, the disease bartonellosis should be included in the differential diagnosis for many patients, particularly those with nonspecific clinical signs, poor responses to symptomatic or short duration antibiotic therapy, deterioration in clinical status following immunosuppression, or when historically the pet was found or rescued as a stray (animals that often have extensive arthropod exposures prior to rescue). As cats and dogs with prior exposure to fleas, ticks and other arthropod vectors are at risk for acquiring *Bartonella* infections, veterinarians should always obtain a comprehensive vector exposure history for sick animals and should determine client compliance if acaricides have been used to prevent arthropod infestations. The fact that a product was dispensed on a routine basis, does not mean that the product was administered or used in the manner recommended by the manufacturer.

The numerous species within the genus *Bartonella*, antigenic and virulence differences among strains, species and subspecies, the diverse cell tropism of these bacteria, their ability to induce persistent occult endotheliotropic and intravascular infections in both reservoir and nonreservoir hosts, and the extraordinarily low levels of relapsing bacteraemia found in accidentally infected, nonreservoir hosts, all contribute to the clinical, microbiological and pathological complexities associated with the diagnosis of bartonellosis in cats, dogs, horses, humans and all other "creatures great and small".[49] Following what in most instances appears to be a persistent dermatological and blood-borne infection, dogs and human patients develop similar disease manifestations (Table 3). Endocarditis, myocarditis, pericarditis, peliosis hepatitis, bacillary angiomatosis, systemic angiomatosis, granulomatous inflammatory lesions in various tissues, lymphadenitis, vasculitis, thromboembolism, cutaneous panniculitis, anterior uveitis, lameness/polyarthritis, splenomegaly and meningoencephalitis have been reported in both dogs and humans, making dogs a useful naturally occurring infectious disease model for human Bartonellosis and vice versa (namely One Health).[15]

Due to the relatively small number of PCR- or culture-confirmed cases overall, few studies have addressed clinicopathological differences induced by different *Bartonella* spp. in cats, dogs, horses or humans. Thrombocytopenia, anaemia, which can be secondary immune-mediated, and neutropenia or neutrophilic leucocytosis are the haematological abnormalities reported in dogs that are *Bartonella* seroreactive or BAPGM enrichment blood culture/PCR positive.[3,21,47] Thrombocytopenia is found in approximately half and eosinophilia in approximately one third of infected dogs, and monocytosis frequently occurs in association with *Bartonella* endocarditis.[2,3] Haematological abnormalities have been rarely reported in cats, but similar to dogs, a subset of *Bartonella*-infected cats are neutropenic or mildly thromobocytopenic.[48]

Serum biochemical abnormalities are usually very mild or nonexistent in healthy and sick bacteraemic cats and dogs. In cats, *Bartonella* spp. antibodies have correlated with polyclonal hyperglobulinaemia and hypoglycaemia.[50] Hyperinsulinemic hypoglycaemia syndrome has been reported in two dogs infected with a *Bartonella* sp.[51] Monoclonal gammopathies have been reported in association with bartonellosis in cats, dogs and humans.[52,53] In a study that compared *Bartonella* bacteraemic dogs to non-*Bartonella* bacteraemic dogs, suspected of a vector-borne infection, hypogammaglobulinemia was the only statistically significant laboratory finding that discriminated between the two groups.[47] Similar to cats and humans, *Bartonella* bacteraemia can be detected in healthy dogs being screened as blood donors.[54] Because *Bartonella* spp. occur as co-infections with other vector-borne organisms, comprehensive serology and PCR testing should be considered when pursuing a diagnosis of vector-borne illness.[52,55–57]

Table 3. Comparative pathological and haematological abnormalities associated with human and canine bartonellosis. Causation has not been clearly established for all of these entities in either species. Details are provided in references 3, 12, 14 and 15.

Abnormality	Human	Dog
Peliosis hepatis	+	+
Bacillary angiomatosis	+	+
Endocarditis	+	+
Myocarditis	+	+
Granulomatous		
lymphadenitis	+	+
hepatitis	+	+
panniculitis	+	+
Anterior uveitis	+	+
Encephalitis	+	+
Thrombocytopenia	+	+
Haemolytic anaemia	+	+

Serology, isolation and molecular detection of *Bartonella* species

Achieving an accurate microbiological diagnosis of bartonellosis can be extremely challenging, particularly in patients with chronic, long standing infections.[49,57] Conventional bacterial isolation techniques, ELISA, Western Blot or IFA detection of *Bartonella* spp. antibodies, and PCR amplification of *Bartonella* spp. DNA directly from patient samples all have diagnostic limitations.[49,56] Due to the fastidious growth requirements of this genus of bacteria, PCR amplification of organism-specific gene fragments is often used diagnostically, particularly when isolation was not successful and serology was negative (a frequent occurrence in bacteraemic dogs and humans). Direct culture of blood and other specimens (cerebrospinal fluid, joint fluid or cavitary effusions) onto blood agar plates from sick dogs or human patients has proven to be diagnostically insensitive.[15,49] Similar to microbiological culture onto blood agar plates, the sensitivity of PCR amplification of *Bartonella* spp. DNA directly from patient samples also is insensitive for the documentation of active infections. Therefore, our research found that enrichment culture of clinical specimens in an optimized, insect cell culture growth medium, prior to PCR testing, substantially increased the sensitivity of detecting infection and diagnosing bartonellosis, see below for more details.[21,49,58–61]

As with other infectious diseases, seroconversion (at least a four-fold rise in antibody titre over a 2–3 week period) can be used to confirm an acute case of bartonellosis. For reasons that remain unclear, antibody reactivity is detected in only 50% of dogs infected with *B. vinsonii* subsp. *berkhoffii* and 25% of dogs infected with *B. henselae*.[21] Research addressing these discrepancies is underway. From a zoonotic and comparative infectious diseases perspective, most dogs, some cats and many *Bartonella* bacteraemic human patients do not have antibodies against the infecting *Bartonella* sp. found in their blood or tissues.[21,48,58,59] Therefore, antibody testing remains highly insensitive. Serology can be used to support a clinical diagnosis; however, the presence of antibodies can only be used to infer prior exposure to a *Bartonella* sp. A seroreactive dog may be actively infected, but studies to characterize the association between serology and active infection in dogs are lacking. Based upon our testing, *B. henselae* and *B. vinsonii*

subsp. *berkhoffii* antibodies are infrequently detected in healthy or sick, well cared for dogs[16,18,54] For this reason, treatment of seroreactive, sick dogs or dogs from which any *Bartonella* spp. is isolated or DNA is detected in blood or tissue samples would be recommended.

Ideally, the microbiological diagnosis of all *Bartonella* infections should be confirmed by culturing the organism from blood, cerebrospinal fluid, joint fluid or aseptically obtained tissues (lymph node, spleen, heart valve) or by PCR amplifying Bartonella DNA directly from diseased tissues, such as skin. When testing cat blood samples, *B. henselae* and *B. clarridgeiae* can often be isolated effectively using agar plates, however, isolation of these same *Bartonella* spp. from dog, horse or human blood samples using an identical isolation approach is very insensitive.[58] Since 2005, we have used BAPGM: this is a novel, chemically modified, insect-based liquid culture medium to support the growth of *Bartonella* species.[58,61] This medium also facilitates documentation of co-infections with more than one *Bartonella* species or with other bacteria.[21,59–61] Obviously, the relative sensitivity of diagnostic methods used to detect *Bartonella* species infection greatly influences the results and interpretation of epidemiological studies, an investigator's ability to establish disease causation, or a clinician's ability to achieve a diagnosis and initiate appropriate treatment. The BAPGM platform combines enrichment culture of a clinical specimen in the liquid growth medium for a minimum of 7 days, followed by a highly sensitive PCR assay designed to amplify all known *Bartonella* species. The combined BAPGM enrichment culture/PCR assay has become the main testing platform utilized by the Intracellular Pathogen Research Laboratory (IPRL), North Carolina State University, USA, for research studies and is available from Galaxy Diagnostics, Inc. (contact@galaxydx.com; Morrisville, NC, USA) to document *Bartonella* infection in animals and immunocompetent or immunocompromised human patients. When compared with more traditional diagnostic methods, this combinational approach has facilitated the detection of canine infections with six *Bartonella* sp. (*B. henselae*, *B. koehlerae, B. quintana*, *B. vinsonii berkhoffii*, *B. bovis* and *Bartonella volans*-like), but of perhaps greater comparative microbiological importance, this approach has resulted in the successful isolation of *B. henselae* (among the only canine-derived isolates to date) from sick dogs.[15,21]

Therapy

To date, an optimal protocol has not been established for the treatment of chronic bartonellosis in cats, dogs or people.[3,15,62–64] Similar to other vector-borne infections, such as anaplasmosis, borreliosis and ehrlichiosis, many acutely infected individuals may eliminate *Bartonella* spp. immunologically at the time of initial infection, without the need for antibiotic administration. If bacteraemia becomes persistent, a long duration of antibiotic administration (4–6 weeks) may be necessary to eliminate a chronic infection regardless of the antibiotic(s) used for treatment. Due to the rapid development of antimicrobial resistance to macrolides (azithromycin), the author no longer recommends this class of antibiotics as sole therapy for treating *Bartonella* infections.[63] Fluoroquinolones in combination with doxycycline are currently being used by the author to treat clinical cases of bartonellosis, while exploring efficacy through experimental infection studies.[62,63] Despite clinical improvement or resolution of disease manifestations, doxycycline alone does not appear to eliminate *B. vinsonii* subsp. *berkhoffii, B. henselae* or *B. clarridgeiae* bacteraemia in cats, dogs or other animal species.[15,62,63] In human endocarditis patients, administration of aminoglycosides at the time of initial diagnosis improves prognosis and decreases morbidity and hospitalization duration.[65]

If seroreactive at the time of initial diagnosis, serum antibody titres decrease rapidly (3–6 months) and are generally no longer detectable in cats and dogs that recover following antimicrobial therapy.[3] Interestingly, seronegative animals with a history of chronic illnesses (presumably chronic *Bartonella* infection) can seroconvert within days to weeks after initiating antibiotic treatment, thereby providing support for a diagnosis of bartonellosis.[3,48] Therefore, post-treatment serology may be a useful adjunct to BAPGM enrichment PCR to determine if a patient is infected (i.e. patients initially seronegative and PCR negative in blood) or if therapeutic elimination of *Bartonella* infections has been achieved (initially seroreactive regardless of PCR status). Whether there is clinical benefit to follow serological or molecular assay results in cats has not been widely studied, but most treated cats do not become seronegative in the short term. Bacteraemia can resolve after treatment or resolve spontaneously in some cats, whereas other cats remain bacteraemic despite 4–6 weeks of antibiotic (documented for several antibiotic regimens) administration, and despite resolution of clinical abnormalities (such as lethargy, inappetence and fever).[48]

Prevention

There is increasing evidence that *Bartonella* species can be transmitted by fleas and ticks to cats, dogs and potentially to human beings.[15,20,66–68] Therefore, minimizing or eliminating flea and tick exposure is perhaps of greater veterinary and public health importance today, than during any previous time in history. After obtaining a blood meal from a *B. henselae*-infected cat, bacteria numbers increase within the flea's intestinal tract and the bacteria remain viable in flea faeces for at least 9 days.[24] Based upon experimental co-housing experiments, direct transmission from *B. henselae* bacteraemic cats to noninfected cats does not occur in the absence of fleas.[6,69,70] This suggests that human contact with cat saliva by licking, biting or scratches is an unlikely source of human infection, unless the claws or saliva are contaminated with viable *B. henselae* flea faeces. Thus, the best current preventive strategy to avoid *Bartonella* spp. infection in pets and their owners is the routine use of acaricide products to avoid flea infestations from occurring in the cat's environment. This conclusion is further supported by a PCR study that amplified *B. henselae* DNA from cat nail bed clippings or saliva, only if the cat was simultaneously infested with fleas.[71] Dogs have occasionally been implicated in the bite transmission of *B. henselae* to

humans and DNA of several *Bartonella* spp. has been amplified from dog saliva specimens[72] In addition, there was a statistical correlation between dog bites in China and seroreactivity to *Bartonella* spp. antigens.[73] In the United States, an estimated 12,000 outpatients are diagnosed with Cat Scratch Disease (CSD is an acute prototypical *B. henselae* human disease presentation) each year, with 500 patients hospitalized.[74] Inpatients were significantly more likely than outpatients to be male and were 50–64 years of age, suggesting the possibility of more severe disease in older patients. Clearly, additional research is needed to assess the risks associated with vector exposure, contact with flea faeces through inhalation or wounds, and pet bites or scratches.

Veterinary clinicians are frequently consulted about flea infestations and flea allergy dermatitis, and therefore understanding the environmental and biological interactions between cat fleas and *Bartonella* spp. is of clinical importance and facilitates zoonotic disease prevention education. In the context of One Health, veterinarians play a critically important public health role in prevention of zoonotic disease transmission through education and communication with clients, physicians and other health professional colleagues. When rigorous flea and tick control measures are instituted, it is highly probable that transmission of *Bartonella* species to pets and their owners will be greatly reduced or eliminated.[6,69,70] In the context of cats, fleas and CSD, flea-infested cats around the world play an important role in scratch transmission of *B. henselae* (and potentially other *Bartonella* spp. as described above), which is the primary or sole bacterial cause of CSD.[3,74]

Public and occupational health considerations

There is increasing evidence to support a potentially important role for *Bartonella* species as a cause of a spectrum of chronic disease manifestations in human patients.[2–4,15,72] Currently, arthropod exposure and animal contact represent the most important risk factors for a human being acquiring an infection with a *Bartonella* spp. Due to extensive contact with a variety of animal species and at times their associated arthropod infestations, veterinary and other animal workers appear to be at occupational risk for bartonellosis because of frequent exposure to *Bartonella* spp.. As a cosnequence, these individuals should exercise increased precautions to avoid arthropod bites, arthropod faeces (i.e. fleas and lice), animal bites or scratches and direct contact with bodily fluids from sick animals.[10,15,59,67–69,75] As *Bartonella* spp. have been isolated from cat, dog or human blood, cerebrospinal fluid, joint fluid, aqueous fluid, seroma fluid and from pleural, pericardial and abdominal effusions, a substantial number of diagnostic biological samples collected on a daily basis in veterinary practices could contain viable bacteria. The increasing number of defined *Bartonella* spp., in conjunction with the high level of bacteraemia found in reservoir-adapted hosts, which represent the veterinary patient population, ensures that all veterinary professionals will experience frequent and repeated exposure to animals harbouring these bacteria. Therefore, personal protective equipment, frequent hand washing, and avoiding cuts and needle sticks have become more important as our knowledge of this genus has improved and various modes of transmission, including needle sticks, have been defined.[76]

Physicians should be educated as to the large number of *Bartonella* spp. in nature, the extensive spectrum of animal reservoir hosts, and the diversity of confirmed and potential arthropod vectors, current limitations associated with diagnosis and treatment efficacy, and the ecological and the medical complexities induced by these highly evolved intravascular, endotheliotropic bacteria. Also, based upon recent microbiological findings, physicians and microbiologists should also be aware of the potential for perinatal and familial infections with one or more *Bartonella* species.[8,77–80] In family clusters reported to date, the route(s) of transmission to or among family members remains unclear and the mode(s) of transmission may vary among and within families depending on environmental, social, microbiological and epidemiological factors. Importantly, pets can serve as sentinels for human exposure and humans can serve as sentinels for pet vector infestations, potentially resulting in longstanding *Bartonella* spp. bacteraemia and complex disease manifestations in both pets and owners.[29,30] In conclusion, a One Health approach to the genus *Bartonella* and the diseases collectively called bartonellosis, should improve animal and human health throughout the world.

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Résumé

Contexte – La bartonellose est une infection zoonotique de distribution mondiale due à un nombre croissant de *Bartonella* spp récemment découvert.

Objectifs – Cette revue permet une mise à jour des aspects médicaux comparatifs de cette maladie, incluant l'épidémiologie, la pathogénie, le diagnostic clinique, le traitement et les difficultés inhérentes à l'atteinte.

Résultats – Par comparaison d'importance médicale, *Bartonella* spp. sont transmis par plusieurs arthropodes vecteurs, comprenant puces, poux, mouches, tiques et potentiellement, acariens et araignées. Avant 1990, il y a avait uniquement une espèce de *Bartonella (B. bacilliformis),* tandis qu'il y en a maintenant plus de 36, dont 17 ont été associées avec un spectre croissant de maladies humaines et animales. Les données récentes des techniques diagnostiques ont facilité la documentation d'atteintes sanguines chroniques et des infections dermatologiques à *Bartonella* spp. Chez l'animal sain et malade, chez l'homme donneur de sang, et les patients humains immunocompétents et immunodéprimés. Le champ de recherche de *Bartonella* reste peu développé et est riche en interrogations, pour lesquelles des réponses aux questions des patients sont cruellement nécessaires. Les recherches de *Bartonella* pourraient substantiellement réduire le spectre des maladies débilitantes et chroniques animales et humaines et ainsi réduire la souffrance à travers le monde.

Conclusion – Une approche One Health à cette maladie infectieuse émergente est clairement nécessaire pour définir les manifestations de la maladie, pour établir la pathogénie comparée de ce pathogène furtif, pour valider les régimes de traitement efficaces et prévenir la transmission de la zoonose.

Resumen

Antecedentes – La bartonelosis es una enfermedad infecciosa zoonótica de distribución mundial, causada por un número cada vez mayor de nuevas especies de *Bartonella spp*.

Objetivos – Esta revisión sirve como una actualización sobre los aspectos médicos comparativos de esta enfermedad, incluyendo la epidemiología, la patogénesis, el diagnóstico clínico, el tratamiento y los retos de las infecciones.

Resultados – De importancia en medicina comparada, *Bartonella spp*. son transmitidas por varios vectores artrópodos, incluyendo pulgas, melófagos, piojos, moscas de arena, garrapatas y, potencialmente, ácaros y arañas. Antes de 1990, sólo había una especie llamada *Bartonella* (*B. bacilliformis*), mientras que ahora hay más de 36, de los cuales 17 se han asociado con un espectro cada vez mayor de enfermedades animales y humanos. Los recientes avances en las técnicas de diagnóstico han facilitado la descripción de infecciones crónicas dermatológicas y sanguíneas con *Bartonella spp*. en animales sanos y enfermos, en donantes de sangre humana y en pacientes humanos inmunocompetentes e inmunocomprometidos. El campo de la investigación de *Bartonella* permanece en su infancia y aun quedan muchas preguntas sin responder, para las cual se necesitan imperiosamente respuestas relevantes para el paciente. La investigación dirigida de *Bartonella* podría reducir sustancialmente un espectro de enfermedades animales crónicas y debilitantes animales y humanas, y así reducir el sufrimiento en todo el mundo.

Conclusión – Un enfoque de salud única para esta enfermedad infecciosa emergente es claramente necesario para definir las manifestaciones de la enfermedad, establecer la patogénesis comparativa de las enfermedades infecciosas de este patógeno poco conspicuo, y validar regímenes de tratamiento eficaces y prevenir la transmisión de enfermedades zoonóticas.

Zusammenfassung

Hintergrund – Die Bartonellose ist eine zoonotische infektiöse Erkrankung mit einer weltweiten Verbreitung, die durch eine zunehmende Zahl von jüngst entdeckten *Bartonella* spp. verursacht wird.

Ziele – Diese Review dient als Update der komparativen medizinischen Aspekte der Erkrankung, wie Epidemiologie, Pathogenese, klinische Diagnose, Behandlung und Herausforderungen.

Ergebnisse – Von komparativer medizinischer Bedeutung ist die Tatsache, dass *Bartonella* spp. von verschiedenen Arthropoden als Vektoren, wie Flöhe, Lausfliegen, Läusen, Sandmücken, Zecken und möglicherweise von Milben und Spinnen übertragen wird. Vor 1990 gab es nur eine *Bartonella* Spezies (*B. bacilliformis*), während es jetzt über 36 gibt, von denen 17 mit einem erweiterten Spektrum von Erkrankungen von Mensch und Tier in Zusammenhang gebracht werden. Jüngste Fortschritte in der Diagnostik haben die Dokumentation chronischer Infektion der Blutwege und dermatologische Infektionen mit *Bartonella* spp. bei gesunden und kranken Tieren, bei menschlichen Blutspendern, sowie bei immunkompetenten und immunkompromittierten Patienten ermöglicht. Die Forschung auf dem Gebiet von *Bartonella* bleibt in den Kinderschuhen und wirft viele Fragen auf, auf die Patienten-relevante Antworten dringend benötigt werden. Eine entsprechend ausgerichtete Forschung auf dem Gebiet der Bartonellae könnte ein ganzes Spektrum von chronischen und debilitierenden Erkrankungen bei Mensch und Tier reduzieren und dabei viel Leiden auf der Welt verhindern.

Schlussfolgerung – Ein One Health Zugang zu diesen neu auftretenden infektiösen Erkrankungen wird dringend benötigt, um Manifestationen von verschiedenen Krankheiten zu definieren, um die vergleichende Pathogenese der infektiösen Erkrankungen dieses versteckten Pathogens zu erforschen, um ein effektives Behandlungsregime zu validieren und um die Übertragung von zoonotischen Erkrankungen zu vermeiden.

要約

背景 – バルトネラ症は世界中に分布する人獣共通感染症であり、Bartonella spp. によって引き起こされる。本病原体は、近年新たに発見された種により、その数を増加させている。

目的 – 本総論では、本疾患の疫学、病因、臨床診断、治療およびその難しさを含めた比較医学の観点から、最新の知見を紹介する。

結果 – – Bartonella spp. はノミ、シラミバエ、シラミ、ブユ、マダニ、そして潜在的にダニやクモなどの様々な媒介節足動物によって伝播されるため、比較医学的に重要である。1990年以前は、Bartonellaと名の付く種は1種(B. bacilliformis)しかいなかったが、現在ではその数は36種を超え、そのうち17種が動物や人の様々な疾患に関与している。近年、診断技術の発達により、健康な動物あるいは病気に罹患した動物、献血者、そして免疫正常者および免疫不全患者における、Bartonella spp. の血液中および皮膚の慢性感染を証明することが容易となった。Bartonella研究はいまだ初期段階にあり、多くの疑問を残してい

る。そのため、患者の立場に即した答えが大いに求められている。正しい方向性を持ったBartonella研究が、慢性的に体を衰弱させる動物および人の疾患を本質的に軽減させ、延いては世界中の罹患数を減らすことになる。
結論 – 本新興感染症の特徴を明らかにし、このステルス病原体による比較感染症病因を解明し、効果的な治療法を確立して人獣共通感染症の伝播を防ぐOne Healthアプローチが明らかに必要とされている。

摘要
背景 — 巴尔通体病是一种分布在全世界的人与动物共患性传染病,由被新发现的大量巴尔通体引起。
目的 — 巴尔 本综述在比较医学方面更新该病信息,包括流行病学、发病机理、临床诊断、治疗和攻毒。
结果 — 巴尔通体比较医学的重要性意义,在于它可以被几种节肢动物媒介传播,包括跳蚤、绵羊蜱、虱子、沙蝇 、蜱虫和潜在的螨虫和蜘蛛。1990年之前,只命名了一种巴尔通体 (B. bacilliformis), 但是现在超过36种,其中17种可引起人和动物的疾病。最近,随着诊断技术的进步,推动更多文献记录了健康和患病动物、人类献血者,以及免疫正常和免疫低下病人和动物的慢性血液和皮肤巴尔通体感染。巴尔通体领域的研究还停留在初期阶段,存在很多待解问题。定向的巴尔通体研究表明,可以缩短慢性发病的时长范围,使动物和人的疾病程度减弱,并且因此而减轻病痛。
结论 — 对于这个新兴传染性疾病,显然需要全球健康一体化方法,以定义其临床症状,建立这种比较性传染病的发病机理,证实有效的治疗方法,并阻止人与动物间的疾病传播。

Resumo
Contexto – Bartonelose é uma doença infecciosa, de caráter zoonótico e distribuição mundial, causada por um número crescente de espécies de *Bartonella spp.* recém descobertas.
Objetivos – Esta revisão tem como objetivo atualizar os aspectos médicos comparativos da doença, incluindo epidemiologia, patogênese, diagnóstico clínico, tratamento e desafios.
Resultados – Relevante na medicina comparada, *Bartonella spp* são transmitidas por diversos vetores artrópodes, incluindo pulgas, piolhos, flebótomos, carrapatos, e, potencialmente, ácaros e aranhas. Antes de 1990, havia apenas uma espécie bacteriana classificada como *Bartonella* (*B. bacilliformis)*, enquanto atualmente existem mais de 36, das quais 17 tem sido associadas a um espectro crescente de doenças em humanos e animais. Avanços recentes nas técnicas de diagnóstico tem facilitado a documentação de infecções hematológicas e dermatológicas por *Bartonella spp.* em animais saudáveis e doentes, em doadores de sangue humanos e em pessoas imunocompetentes e imunodeprimidas. O campo de pesquisa de *Bartonella spp.* permanece em sua fase inicial e é repleto em perguntas, para as quais, respostas relevantes para os pacientes são imprescindíveis. Pesquisas específicas com *Bartonella* poderiam reduzir substancialmente o espectro de doenças crônicas e debilitantes em humanos e animais, e, assim, reduzir o sofrimento mundialmente.
Conclusão – A abordagem conhecida como *One Health* para esta doença infecciosa emergente se faz claramente necessária para se compreender suas manifestações clínicas, estabelecer estudo comparado da patogênese da enfermidade causada por este patógeno silencioso, validar protocolos de tratamento eficazes e prevenir a transmissão zoonótica da doença.

