Bartonellosis: One Health Perspectives for an Emerging Infectious Disease

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Abstract

In recent years, an increasing number of *Bartonella* species have been identified as zoonotic pathogens, transmitted by animal bites, scratches, arthropods and even by needle sticks. Considering the diversity of newly discovered *Bartonella* species and subspecies and the large number and ecologically diverse animal reservoir hosts and the evolving spectrum of arthropod vectors that can transmit these bacteria among animals and humans, the clinical and diagnostic challenges posed by *Bartonella* transmission in nature are presumably much more complex than is currently appreciated by diagnosticians, vector biologists, ecologists, physicians, or veterinarians. Historically the term "bartonellosis" was attributed to infections with *Bartonella bacilliformis,* transmitted by sandflies in the Peruvian Andes. Currently, however, bartonellosis now includes infections caused by any *Bartonella* sp. anywhere in the world. Potentially, because *Bartonella* spp. can infect erythrocytes, endothelial cells, pericytes, $CD34^+$ progenitor cells, and various macrophage-type cells, including microglial cells, dendritic cells, and circulating monocytes in vitro, the clinical and pathological manifestations of bartonellosis appear to be very diverse in both sick animals and human patients. Because 75% of emerging infectious diseases are zoonoses, many of which are vector-transmitted by an arthropod, a One Health approach to bartonellosis and other zoonotic infections is needed to properly address animal health, public health, and environmental factors that influence the distribution and transmission of these bacteria. The One Health concept encourages a spirit of cooperation among animal, environmental, and human health professionals and promotes developing integrated solutions for complex problems that impact the health of animals, humans, and the planet. Importantly, substantial research is needed to define the medical importance of this genus as a cause of animal and human illnesses.

Key Words: animals; bacteria; *Bartonella*; bartonellosis; disease; One Health; reservoirs; vectors

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Introduction

Because of rapid changes in microbiological, pathophysiological, and medically relevant information regarding bartonellosis, One Health professionals, including ecologists, environmentalists, microbiologists, physicians, vector biologists, and veterinarians, have published numerous authoritative reviews during the past two decades, of which a subset are cited (Billeter et al. 2008; Boulouis et al. 2005; Breitschwerdt and Kordick 2000; Breitschwerdt et al. 2010a; Chomel et al. 2006; Harms and Dehio 2012; Kaiser et al. 2011; Minnick and Battisti 2009). *Bartonella* species are recently rediscovered, fastidious, Gram-negative, vector-borne bacteria that are highly adapted to one or more mammalian reservoir hosts and within which these bacteria have most probably coevolved to cause a long-lasting, relapsing, intraerythrocytic bacteremia (Harms and Dehio 2012; Kaiser et al. 2011). Each of these factors is of particular importance to physicians, veterinarians, and other public health professionals because an increasing number of animal reservoir hosts and a diversity of arthropod vectors have been identified for both the environmental maintenance and competent transmission of various *Bartonella* species (Table 1). Among numerous other examples, *Bartonella henselae* has coevolved with cats, *Bartonella vinsonii* subsp. *berkhoffii* has coevolved with dogs and wild canines, *Bartonella bovis* has coevolved with cattle, Candidatus *Bartonella melophagi* has coevolved with sheep, and *Bartonella australis* has coevolved with kangaroos (Chomel et al. 2006; Guy et al. 2013). Thus, a diversity of *Bartonella* spp. have most likely coevolved with specific animal species and the arthropods that have historically infested these animals. Importantly, the list of mammalian reservoir-adapted *Bartonella* species, including an extremely large number of rodent-adapted *Bartonella* spp. that might serve as "pocket pets," continues to grow exponentially as new *Bartonella* spp. have been discovered (Buffet et al. 2013). Examples of closely related rodent *Bartonella* spp. include proposed Candidatus species that have coevolved with ground squirrels (Candidatus *Bartonella washoensis*), gray squirrels (Candidatus *Bartonella durdenii*), flying squirrels (Candidatus *Bartonella volans*), and ground hogs (Candidatus *Bartonella monaxi*). Most recently, a diversity of novel *Bartonella* spp. have been identified in insectivorous and frugivorous bats, which may ultimately prove to be of zoonotic, One Health

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Table 1 Species and subspecies of *Bartonella* that are confirmed or potential human pathogens, primary hosts and vectors, known accidental hosts, and human diseases

Bartonella	Primary reservoir	Vector	Accidental host(s)and [human disease]
Bartonella alsatica	(Rabbit *Oryctolagus cuniculus*)	(Rabbit flea? *Spilopsyllus cuniculi*)	Human (endocarditis)
Bartonella bacilliformis	Human	(Sandfly *Lutzomia verrucarum*)	None [Carrion's disease, Oroya fever, verruga peruna]
Bartonella clarridgeiae	(Cat *Felis catus*)	(Cat flea *Ctenocephalides felis*)	Human, dog [cat scratch disease/ endocarditis]
Bartonella elizabethae	(Rat *Rattus norvegicus*)	(Oriental rat flea *Xenopsylla cheopis*)	Human, dog [endocarditis, neuroretinitis]
Bartonella grahamii	(Wild mice *agrestris, Apodemus Clethrionomys glareolus, Microtus flavicollis*)	Rodent fleas	Human [neuroretinitis]
Bartonella henselae	(Cat *Felis catus*)	(Cat flea *Ctenocephalides felis*)	Human, dog, horse, marine animals [Cat scratch disease, bacillary angiomatosis, endocarditis, neuroretinitis, bacteraemia
Bartonella koehlerae	Cat	Cat flea	Human, dog [endocarditis]
Bartonella melophagi	(Sheep *Ovis aries*)	(Sheep ked *Melophagus ovinus*)	Human [pericarditis, chronic fatigue]
Bartonella quintana	Human	(Body louse *Pediculus humanis*)	Cat, dog [endocarditis, trench fever, bacillary angiomatosis]
Bartonella rochalimae	Canids	(Fleas? *Pulex irritans*, *Pulex simulans*)	Human, dog [bacteraemia, fever]
Bartonella tamiae	(Rat?) Unknown	Mites? Ticks?	Humans [bacteraemia, fever]
Bartonella vinsonii arupensis	(White-footed mouse *Peromyscus leucopus*)	(Fleas? ticks?) Unknown	Human [bacteraemia, fever, endocarditis]
Bartonella vinsonii berkhoffii	(Coyote *Canis latrans*) Dog (*Canis familiaris*)	(Ticks?) Unknown	Human, cat [endocarditis]
Bartonella washoensis	(Californian ground squirrel *Spermophilus beecheyii*)	(Fleas *Oropsylla montana)*	Human, dog [myocarditis, endocarditis]

Adapted from Chomel BB, Kasten RW. 2010. Bartonellosis, an increasingly recognized zoonosis, J Appl Microbiol 109 : 743–750; and Kaiser PO, Riess T, O'Rourke F, Linke D, Kempf VA. 2011. *Bartonella* spp.: Throwing light on uncommon human infections. Int J Med Microbiol 301 : 7–15.

importance (Bai et al. 2012b; Mühldorfer 2013). It is also increasingly obvious that bats have coevolved with a large number of bacterial and viral zoonotic pathogens, further increasing the medical importance of bat bites and, potentially, exposure to bat guano (Mühldorfer 2013).

Before 1990, there was only one named *Bartonella* species (*B. bacilliformis*), whereas there are now at least 30 named and numerous yet to be named or Candidatus species. Seventeen *Bartonella* spp. have been associated with an expanding spectrum of animal and human diseases (Breitschwerdt et al. 2010a; Harms and Dehio 2012; Kaiser et al. 2011). Considering the diversity of newly discovered *Bartonella* species and subspecies, the large number and diversity of animal reservoir hosts, and the spectrum of transmission competent and implicated arthropod vectors, the clinical and diagnostic challenges posed by *Bartonella* transmission in nature are presumably much more complex than is currently appreciated by microbiologists, physicians, veterinarians, and vector biologists (Cherry et al. 2011; Mascarelli et al. 2013).

Historical Highlights

Although historically the term "bartonellosis" was attributed to infections with *B. bacilliformis,* transmitted by sandflies (genus *Lutzomyia*) in the Peruvian Andes, a more inclusive medical use of this term now includes infections caused by any *Bartonella* sp. anywhere in the world. Before 1990 and the discovery of the AIDS virus, *Bartonella* spp. were not

recognized as animal or human pathogens in North America and, to a substantial degree, throughout the world. During the early years of the AIDS epidemic, bacteria were histopathologically visualized with silver stains within bacillary angiomatosis and peliosis hepatis lesions (i.e., vasoproliferative lesions within the skin or liver, respectively) of immunocompromised individuals (Koehler et al. 1997; Moulin et al. 2012; Relman et al. 1992). Because initial efforts to isolate these bacteria were unsuccessful, Dr. David Relman and colleagues (1992) at Stanford University amplified 16S rDNA sequences from bacillary angiomatosis tissues that were consistent with *Bartonella quintana* and a second, not previously described bacterium, which ultimately was shown to be *B. henselae,* and subsequently shown to be the cause of cat scratch disease (CSD). Historically, two medically important *Bartonella* spp. (i.e., *B. bacilliformis* and *B. quintana*) predated the "rediscovery" of *Bartonella* spp. as a cause of animal and human diseases in North America and throughout the world. Subsequently, the association of *B. henselae* with CSD by Russ Regnery at the Centers for Disease Control and Prevention in Atlanta, Georgia, resulted in the recognition that numerous cats throughout the world were *B. henselae* bacteremic and that *Ctenocephalides felis* (the "common" cat flea) was responsible for bacterial transmission among cats (Pennisi et al. 2013; Zangwill 2013) In addition, circumstantial historical evidence supports the potential that flea bites (cat, dog, and rodent fleas) may result in direct transmission of several *Bartonella* spp. to humans (Bouhsira et al. 2013; McElroy et al. 2010). Importantly, recent in vitro evidence supports the ability of five *Bartonella* species to persist in *C. felis,* suggesting an ability of the common cat flea to be a potential vector for several *Bartonella* species (Bouhsira et al. 2013; Yore et al. 2014). In the context of other recent research observations and daily medical practice, it seems likely that cat flea transmission of pathogenic *Bartonella* spp. throughout much of the world poses a substantially greater infectious disease risk for animals and humans than is currently appreciated. Recent experimental laboratory evidence also indicates that the routine use of an acaracide product can interrupt flea transmission of *B. henselae* to cats, which would prevent cat transmission of these bacteria to humans (Lappin et al. 2013). Currently, no vaccines are available to prevent *Bartonella* infections in animals or humans.

Carrion's Disease

Although archeological evidence supported infection in indigenous Peruvians hundreds of years earlier, infection with *B. bacilliformis* was first published in 1909 by Alberto Barton (Sanchez Clemente et al. 2012). This bacterium causes both an acute febrile illness (Carrion's disease or Oroya fever) and a chronic vasoproliferative disease (verruga peruana) and is primarily diagnosed in people from Peru, Ecuador, and Columbia, but it has also been described in travelers to South America months to years after returning to nonendemic countries. In the acute illness, usually occurring within 21 days of an infected sandfly bite, there is a severe intravascular hemolytic anemia, with symptoms of high fever, anemia, and temporary immunosuppression, lasting from two to four weeks. When *B. bacilliformis* invades endothelial cells, nodular skin lesions begin to appear; these lesions can be pruritic and bleed spontaneously or if abraded. Immunosuppression, secondary to *B. bacilliformis*, resulting in tuberculosis and other coinfections, has also been suggested to occur in association with long-standing intravascular *B. bacilliformis* infection resulting in verruga peruana (Pulliainen and Dehio 2012). Importantly, potential immunological consequences, such as immune suppression, associated with persistent infection with *B. bacilliformis* and other *Bartonella* spp. have not been reported.

Trench Fever

B. quintana, first isolated in 1960 by J.W. Vinson, also causes both acute (trench fever) and chronic (endocarditis and bacillary angiomatosis) disease processes (Bonilla et al. 2009; Brouqui and Raoult 2006). This species is best known for causing illness in more than one million soldiers fighting during World War I in Europe. The acute disease (trench fever) is characterized by fever, headache, and leg pain (shin bone disease) subsequent to the bite of an infected human body louse (*Pediculus humanus humanus*). Alternatively, infection was experimentally induced in human volunteers during World War I by applying louse feces or saliva from an infected febrile trench fever patient to abraded skin. The incubation period for trench fever ranges from 5 to 20 days. Because *B. quintana* can invade erythrocytes and endothelial cells, bacillary angiomatosis, a chronic *B. quintana* disease manifestation that causes cutaneous nodular lesions protruding from the vascular lamina, can occur in immunocompromised individuals. In 1992, *B. quintana* was demonstrated to cause endocarditis, which is a medical concern for human immunodeficiency virus–infected patients and other immunocompromised individuals, homeless persons, and alcoholics/substance abusers who are at higher risk of human body louse exposure and persistent *B. quintana* bacteremia (Brouqui and Raoult 2006). *B. quintana* DNA has been amplified from cat fleas, and the bacteria was isolated from a woman residing in North Carolina and from the feral cat that induced her bite wound, supporting the possibility of cat bite transmission of this *Bartonella* sp. and human infection by modes other than body louse exposure (Breitschwerdt et al. 2007).

Cat Scratch Disease

For more than a century, fever and regional lymphadenopathy have been associated with animal contact, particularly cat scratches (Zangwill 2013). During the late 1900s, numerous microorganisms, including *Afipia felis*, were implicated as the cause of CSD. Before the recognition of *B. henselae* as the

cause of CSD, *A. felis*, named for the Armed Forces Institute of Pathology, was considered the sole cause of CSD. Subsequent research indicates that *A. felis* is an infrequently identified cause of human febrile illness and lymphadenopathy. Then, in 1992, Regnery and colleagues at the Centers for Disease Control identified seroreactivity to *B. henselae* antigens in 88% of 41 human patients with suspected CSD compared with 3% of healthy control subjects. Subsequently, additional support for *B. henselae* as the predominant cause of CSD was provided when *Bartonella* DNA was amplified using a polymerase chain reaction (PCR) assay from lymph node samples of 21 of 25 (84%) patients with suspected CSD (Anderson et al. 1994). A similar study from Sweden identified *B. henselae* DNA, but failed to identify *A. felis* DNA (a historically proposed cause of CSD), in a large number of patients with suspected CSD. Subsequently, we cultured *B. henselae* or *Bartonella clarridgeae* from the blood of 17 of 19 cats owned by 14 CSD patients weeks to years after CSD was diagnosed in the owner or bite/scratch victims, which indicated that chronic bacteremia is a frequent occurrence in cats that transmit *B. henselae* to a human being (Kordick et al. 1995). However, recent microbiologic evidence indicates that the most common *B. henselae* genotypes found in bacteremic cats are not the same genotypes found in CSD patients, suggesting that only a subset of the more virulent *B. hensleae* strains found in cats causes acute CSD (Chaloner et al. 2011).

Historically, atypical manifestations of CSD have included tonsillitis, encephalitis, cerebral arteritis, transverse myelitis, granulomatous hepatitis and/or splenitis, osteolysis, pneumonia, pleural effusion, and thrombocytopenic purpura. With the advent of more specific and sensitive diagnostic techniques (culture, serology, PCR, enrichment culture/PCR), there has been a dramatic increase in reports describing human patients with "atypical" manifestations of CSD, suggesting that these atypical manifestations occur much more commonly than was historically suspected (Giladi et al. 2005; Zangwill 2013). In particular, osteomyelitis, granulomatous hepatitis, and granulomatous splenitis have been increasingly recognized in children and adults infected with *B. henselae.* A large subset of these patients lacks the classical fever and lymphadenopathy associated with typical CSD. Therefore, until recently, *Bartonella* infection would not have been considered a likely differential diagnosis by a physician in patients lacking a history of fever, lymphadenopathy, and cat contact. As evidenced by reports in the past 4 years, the spectrum of human disease associated with the genus *Bartonella* continues to expand, requiring periodic reassessment as new information becomes available (Breitschwerdt et al. 2010a; Harms and Dehio 2012; Kaiser et al. 2011; Zangwill 2013). On a comparative medical (One Health) basis, our research group has documented many of the same human atypical CSD manifestations in sick cats or dogs, including encephalitis, transverse myelitis, granulomatous hepatitis, osteolysis, pleural effusion, and thrombocytopenic purpura (Breitschwerdt et al. 2010a; Cherry et al. 2009; Varanat et al. 2009). In the context of One Health, the atypical manifestations of a highly prevalent, naturally occurring human disease (CSD) were used as a naturally occurring model to determine the potential behavior of the genus *Bartonella* in companion animal patients (cats and dogs), ultimately resulting in documentation of comparable pathologies.

Typical CSD historically denotes a self-limiting illness characterized by fever and lymphadenopathy, temporarily associated with a cat scratch or bite. Because of the recognized spectrum of human disease manifestations associated with bartonellosis (which does not consistently include fever, lymphadenopathy, or a history of an animal bite or scratch) and because a subset of CSD patients develop persistent bacteremia, it is becoming obvious that although a commonly used term in the clinical setting, the designation CSD has much more limited clinical, microbiologic, and zoonotic utility than could be appreciated a few short years ago. Although cats are a major reservoir for *B. henselae, B. clarridgeiae*, and *Bartonella koehlerae,* some CSD patients deny the possibility of a cat scratch or bite wound or indicate no contact with cats. Clinical evidence indicates that transmission of *B. henselae* from environmental sources (historically CSD was associated with rose thorn scratches and *B. henselae* is viable in flea feces for at least 7 days), transmission by various arthropod vectors (Maggi, Ericson, et al. 2013; Mascarelli et al. 2013), perinatally (Breitschwerdt et al. 2010b), or by other animal hosts (Beard et al. 2011; Maggi et al. 2008) is probable; therefore, from an educational and clinical perspective, the more inclusive term bartonellosis may facilitate more rapid future understanding of the pathophysiology, clinical diagnostic paradigms, and diseases caused by members of the genus *Bartonella*. Because physicians have been taught that CSD is self-limiting, there is an ongoing lack of appreciation that *B. henselae* can cause chronic, asymptomatic, minimally symptomatic, or intermittently symptomatic illnesses, accompanied by persistent bacteremia, in people. In this context, the documentation of chronic, relapsing bacteremia in cats (Kordick and Breitschwerdt 1997) and experimentally infected rodent species (Schülein et al. 2001) provides models for enhanced understanding of the potential microbiological aspects of human bartonellosis.

Bartonella Endocarditis

Before 1993, *Bartonella* spp. had never been implicated in or associated with endocarditis in animals or human patients (Chomel et al. 2009). Subsequently, since 1993, endocarditis has been associated with a spectrum of *Bartonella* spp., particularly in dogs and human patients. In the context of disease causation, endocarditis has now been associated with nine and seven *Bartonella* spp. in humans and dogs, respectively, thereby supporting an important pathological role for this genus of bacteria in immunocompetent animals and human patients (Lamas et al. 2013). Historically, because of the highly fastidious nature of these bacteria, *Bartonella* spp. were a cause of culture-negative endocarditis in dogs and people.

Culture-negative endocarditis is diagnosed when echocardiography or valvular histopathology readily documents a heart valve infection but bacteria are not successfully isolated from the patient's blood or valvular tissue. In most instances, historical diagnostic methods used by microbiology laboratories were not adequate to isolate these bacteria. Clearly, successful isolation of *Bartonella* spp. from bacteremic animal and human patients remains an ongoing challenge. However, by using specialized isolation and PCR amplification techniques, research and diagnostic laboratories throughout the world have identified a spectrum of *Bartonella* spp. in reservoir hosts, known and potential vectors, and animal and human patient samples. PCR amplification of *Bartonella* spp. DNA from heart valves or blood culture isolation of these bacteria from dogs and people with echocardiographic evidence of endocarditis has substantially contributed to the expanding spectrum of medically important *Bartonella* spp. that are capable of inducing disease. From a One Health perspective, it is important for physicians to recognize that those *Bartonella* spp. implicated in association with human endocarditis have been found in the blood of cats, dogs, rats, ground squirrels, rabbits, and numerous other animals, many of which serve as persistently bloodstream-infected reservoir hosts and a source of vector transmission and inadvertent human infection (Chomel et al. 2009). Medically, it is imperative for clinicians to obtain a detailed travel history because many *Bartonella* spp. have regional differences in prevalence or occurrence. Also, patient histories should include questions relative to prior exposure to animals and arthropod vectors that infest various animals, particularly rodent and cat fleas, lice, and ticks.

Veterinary Medical Importance

Although the literature is not exhaustive, the clinical and pathological manifestations of bartonellosis in animals (Breitschwerdt et al. 2010a; Pérez Vera, Diniz, et al. 2013) and humans (Breitschwerdt et al. 2012; Florin et al. 2008; Lamas et al. 2008) have been reviewed. Pet cats and dogs often develop very similar or the same disease manifestations as human patients (Beerlage et al. 2012; Breitschwerdt et al. 2010a; Chomel et al. 2009). Because of extensive contact with a spectrum of healthy and sick animal species, veterinary and other animal health professionals appear to have an occupational risk of infection (Breitschwerdt et al. 2008; Breitschwerdt et al. 2010c; Breitschwerdt et al. 2010d, Maggi et al. 2011). Because of frequent exposure to *Bartonella* spp., these individuals should exercise increased precautions to avoid arthropod exposure (i.e., fleas and lice), animal bites or scratches, and direct contact with bodily fluids, particularly from, but not limited to, sick animals. After putative needle stick transmission of a *Bartonella* sp., headache, fatigue, and intermittent paresthesia have been reported in a veterinarian from the United States (Oliveira et al. 2010) and fever of unknown origin and back pain were reported another veterinarian from Taiwan (Lin et al. 2011). In the US veterinarian, all symptoms resolved after antibiotic treatment. Complex regional pain syndrome occurred in a veterinarian, seemingly accompanied by a positive therapeutic response to antibiotics (Pérez Vera et al. 2014). Because *Bartonella* spp. have been isolated from cat and dog blood, cerebrospinal fluid, joint fluid, aqueous fluid, seroma, and pleural, pericardial, and abdominal effusions, a substantial number of diagnostic biological samples collected on a daily basis in veterinary practices could contain viable *Bartonella* sp. bacteria. The increasing number of defined *Bartonella* spp. found in the typical veterinary patient population (cats, dogs, cows, horses, rodents, and other animals) ensures that most veterinary professionals will experience frequent and repeated exposure to animals harboring these bacteria. In addition, there is increasing evidence to support coinfection with *B. henselae* and other bacterial pathogens that induce potentially persistent bloodstream infections in human patients (Cadenas et al. 2007; Maggi, Compton, et al. 2013; Maggi, Mascarelli, et al. 2013; Sykes et al. 2010). Therefore, personal protective equipment, frequent hand washing, and avoidance of cuts and needle sticks have become more important for animal health professionals and others with frequent animal contact, as our knowledge of this genus has improved and various modes of transmission have been better defined.

Human Health Importance

A complete review of novel discoveries related to human bartonellosis is beyond the scope of this article. Because research from my laboratory was among the first to confirm long-standing bacteremia with pet-associated *Bartonella* spp. in nonimmuncompromised human patients, our research findings were clearly unexpected and novel and, as a result, became controversial. Work from Dr. Michael Kosoy's Laboratory and Didier Raoult's Laboratory is also highlighted herein. Important observations from many other clinicians and research groups around the world are acknowledged but cannot be considered because of space limitations.

Initially, we described *B. quintana* bacteremia in a woman who was tested after the development of an infected cat bite lesion involving the hand (Breitschwerdt et al. 2007). Two months later, the feral cat that had induced the bite wound was captured and was also shown to be *B. quintana* bacteremic. In a cumulative study involving 392 patients with occupational animal contact or extensive arthropod exposure (Maggi et al. 2011), 31.9% were bacteremic with one or more *Bartonella* spp. when blood, serum, and *Bartonella* alpha *Proteobacteria* growth medium (BAPGM) enrichment culture PCR results were combined. Although this high prevalence of bacteremia is biased by testing at-risk, sick individuals using a sensitive enrichment culture/PCR/DNA sequencing approach, it clearly demonstrates that intravascular infection with *Bartonella* spp. is much more common in nonimmunocompromisted people than was previously suspected. By immunofluorescent antibody testing, only 75 of 128 (58.6%) PCR-positive individuals were

seroreactive to a panel consisting of five *Bartonella* sp. test antigens. Seronegative *Bartonella* sp. bacteremia appears to be a common and, as yet, unexplained entity in cats, dogs (Perez et al. 2010), and human patients (Maggi et al. 2011). Coinfection with *B. henselae* and a hemotropic *Mycoplasma,* similar or identical to *Mycoplasma ovis,* were also found in the blood of a veterinarian with a historical diagnosis of multiple sclerosis (Sykes et al. 2010). In another study, *Bartonella vinsonii* subsp. *berkhoffii, Bartonella henselae*, or DNA of both organisms was amplified and sequenced from blood, BAPGM enrichment blood cultures, or autopsy tissues from four family members. Historical and microbiological results derived from this family supported the possibility of human perinatal transmission of *Bartonella* spp. (Breitschwerdt et al. 2010b). Interestingly, the parents of these children, both infected with the same *Bartonella* sp. and genotype had attempted to conceive children for several years before resorting to in vitro fertilization. To date, there have been a limited number of studies that address the potential impact of intravascular infection with a *Bartonella* sp. on reproductive performance; however, from a One Health perspective, studies involving experimentally infected cats, rodents, and naturally infected cows with various *Bartonella* spp. have identified a spectrum of reproductive abnormalities, including decreased reproductive performance involving both male and female cats (Guptill et al. 1998). In the context of *Bartonella* spp. and vasoproliferative pathologies, *B. vinsonii* subsp. *berkhoffii* genotype II was amplified and sequenced from a liver biopsy from a young man with epithelioid hemangioendothelioma, after which the organism was isolated by BAPGM blood culture (Breitschwerdt et al. 2009). Subsequently, *B. henselae* and *B. koehlerae* DNA was documented in two additional epithelioid hemangioendothelima patients, one residing in Australia and the other in England. (Mascarelli et al. 2011) *Bartonella* spp. also appear to be associated with vasoproliferative tumors in animals (Beerlage et al. 2012). The unique capability of *Bartonella* to invade and induce long-lasting intraerythrocytic and intraendothelial infections, in conjunction with the ability of at least four *Bartonella* spp. (*B. henselae*, *B. quintana*, *B. bacilliformis,* and *B. vinsonii* subsp. *berkhoffii*) to induce VEGF-mediated vasoproliferative disease in immunocompromised or immunocompetent cats, dogs, humans, and other animals, suggests that these novel emerging bacterial pathogens might contribute to the development of vascular lesions, including vascular tumors in immunocompetent animal and human patients. On a One Health basis, satisfying the Postulate of Comparative Infectious Disease Causation (Breitschwerdt et al. 2013) for *Bartonella* spp. and vasoproliferative tumors may facilitate more rapid medical progress relative to *Bartonella* spp. and oncogenesis involving the vasculature.

Although infrequently implicated as a cause of human infections, *B. koehlerae* bacteremia was documented in eight immunocompetent patients by PCR amplification and DNA sequencing, either before or after BAPGM enrichment blood culture (Breitschwerdt et al. 2010d). Presenting symptoms among these eight patients most often included fatigue, insomnia, joint pain, headache, memory loss, and muscle pain. Although these symptoms are nonspecific and can be associated with numerous infectious and noninfectious diseases, similar symptomatology has been reported in bartonellosis patients in two subsequent case series (Maggi et al. 2011; Maggi et al. 2012). Four *B. koehlerae* bacteremic patients were also infected with *B. vinsonii* subsp. *berkhoffii* genotype II, which may be related to flea transmission of both of these bacteria (Yore et al. 2014). *Bartonella koehlerae* antibodies were not detected (titers < 1 : 16) in 30 healthy human control sera, whereas five of eight patient samples had *B. koehlerae* antibody titers of 1 : 64 or greater. In a subsequent case report, persistent *B. koehlerae* bactermia was documented in a young woman with hallucinations, peripheral visual loss, and a sensory neuropathy (Breitschwerdt et al. 2011) and in a veterinarian diagnosed with complex regional pain syndrome (Pérez Vera et al. 2013). Based upon these case reports and case series, long-term prospective case–control studies are needed to determine whether *B. koehlerae*, *B. henselae*, and other *Bartonella* spp. are a cause or cofactor in the development of arthritis, peripheral neuropathies, or tachyarrhythmias in human patients.

Dr. Michael Kosoy's research group at the Centers for Disease Control and Prevention has investigated zoonotic *Bartonella* spp. infections in patients from Thailand. DNA of numerous rodent *Bartonella* spp., including *Bartonella tamiae*, *Bartonella elizabethae*, *Bartonella tribocorum*, *Bartonella rattimassilensis*, and *B. vinsonii* subsp. *arupensis*, was found in febrile patients who reported recent rodent contact, followed by fever, myalgia, dizziness, headaches, and fatigue (Kosoy et al. 2010). In addition to also documenting human Bartonella endocarditis (*B. henselae*) in Thailand, infection with *B. vinsonii* subsp. *arupensis* was also reported in three febrile patients and another nonfebrile patient whose symptoms included joint pain, abdominal pain, fatigue, myalgia, and cough (Bai et al. 2012a). Because *B. vinsonii* subsp. *arupensis* and other rodent-associated *Bartonella* spp. found in febrile human patients were previously described in bacteremic dogs (Bai et al. 2010), the vector ecology and transmission dynamics of these bacteria among dogs and humans deserve additional research consideration, further emphasizing a One Health approach to bartonellosis as an emerging infectious disease.

Publications from Professor Didier Raoult's research group have provided insights into the human medical importance of *Bartonella* spp. in Europe and other parts of the world. Repeatedly, his laboratory has defined an important role for *B. quintana* and *B. henselae* as a cause of culture-negative endocarditis (Casalta et al. 2009). In addition, the laboratory reported cases of generalized granulomatous lymphadenitis (CSD) in association with *B. henselae.* Both endocarditis and granulmoatous lymphadenitis were subsequently associated with human *B. alsatica* infections in France, most likely due to transmission from rabbits, the reservoir host for this *Bartonella* sp. to humans (Jeanclaude et al. 2009). In a recent publication, 340 of 1688 (53%) lymph nodes from lymphadenitis cases examined at a major referral hospital in France

between 2008 and 2012 contained *B. henselae* DNA (Safont et al. 2014).

As discussed herein, the association of infection with *Bartonella* spp. and vasoproliferative lesions (bacillary angiomatosis and peliosis hepatis) in immunocompromised AIDS patients precipitated research investigations, now spanning more than two decades. Recent reports indicate that bartonellosis is a concern for solid organ transplant recipients (Moulin et al. 2012; Rostad et al. 2012) and patients receiving immunosuppressive drugs for treatment of autoimmune and immune-mediated diseases (Mathieu et al. 2007; Milin et al. 2013). There are also recent case reports describing *B. henselae* infection mimicking autoimmune disease (Maritsi et al. 2013), potentially triggering autoimmune thyroiditis in a child (Chiuri et al. 2013).

The spectrum of symptoms and pathology reported in patients with bartonellosis continues to expand much more rapidly than our understanding of the pathophysiology of many of these disease manifestations. This overview is in no way comprehensive in the context of the evolving literature related to this genus of bacteria but illustrates several major trends related to this emerging pathogen.

Vectors, Environment, Pathogens, and Disease

Epidemiological evidence and experimental transmission studies support an important role for fleas (*C. felis*) in the transmission of these bacteria among cats, dogs and other small mammals throughout much of the world (Billeter et al. 2008). *C. felis* transmits *B. henselae*, *B. clarridgeae*, *B. koehlerae*, and potentially *B. quintana* (Breitschwerdt et al. 2007; Kernif et al. 2014); thus this common ectoparasite should be considered a major source of zoonotic *Bartonella* sp. transmisison. Currently, in the context of a global health threat, flea infestations on pets and feral and wild animals are medically underappreciated as a source of *Bartonella* sp. transmission and as a cause of animal and human suffering/disease. Cats can be chronically bacteremic with four zoonotic *Bartonella* spp. for months to years after flea transmission, making flea-exposed cats a major reservoir for human infection. In addition to fleas, an increasing number of arthropod vectors, including biting flies, keds, lice, mites, sandflies, spiders, and ticks have been implicated in the transmission of *Bartonella* spp. (Billeter et al. 2008, Previte et al. 2014). Wood louse hunter spider bite transmission of *B. henselae* may have resulted in neurological disease manifestations in three members of a family in Kentucky (Mascarelli et al. 2011). Collectively, there are many deficiencies in our understanding of vector competence and mode(s) of *Bartonella* sp. transmission.

Need for a One Health Approach to Bartonellosis

One of the most pressing requirements in the context of Bartonella research is the need to define the biological price, if any, that various animals, including humans, pay for persistent *Bartonella* sp. bloodstream infections. It is unlikely that the answers to this question can be generated through laboratory rodent studies, in vitro cell culture studies, or short-term infection studies. Long-term epidemiological studies or other approaches will be required, such as the recently proposed Postulate of Comparative Infectious Diseases Causation (Breitschwerdt et al. 2013). The original and the more recently proposed molecular Koch's postulates for infectious disease causation have been historically useful, particularly when attempting to confirm that a disease is caused by a single infectious agent that induces an acute infection (frontal pathogen). Establishing disease causation in association with chronic, occult infections caused by "stealth" pathogens such as *Bartonella* spp. that can seemingly induce chronic, slowly progressive disease manifestations in an animal or human patient is much more difficult to achieve by applying the classical or more recently proposed molecular Koch's postulates. In contrast with stealth pathogens, frontal pathogens are characterized by an organism that has a brief incubation period and a readily defined source of exposure/infection and induces an acute illness. In addition to other obvious limitations, rodent and other laboratory-based studies do not readily allow researchers to address naturally occurring environmental, nutritional, genetic, or other medically relevant factors that influence disease causation or consider the pathogenic complexities induced by sequential or simultaneous infection with more than one pathogenic microorganisms, as occurs in nature. This is important because there is evolving evidence of coinfection with other vector-borne organisms, such as *Anaplasma platys* and hemotropic *Mycoplasma* spp. in humans infected with *B. henselae* (Maggi, Compton, et al. 2013; Sykes et al. 2010). Because of these inherent limitations, a group of human and veterinary clinician scientists recently proposed the addition of a fifth Koch's postulate: Causation can be established, if the same infectious agent (or combination of agents) are isolated or organism-specific DNA sequences are amplified from a similar or identical naturally occurring pathological entity found in at least three different mammalian species. In the context of *Bartonella* spp., this postulate has been satisfied for chronic bacteremia, endocarditis, granulomatous inflammatory lesions, and vasoproliferative lesions of the skin and paryenchmal organs (Breitschwerdt et al. 2013).

Because approximately 70% of emerging infectious diseases are zoonotic in nature (Sander et al. 1998), understanding the comparative biological and pathological behavior of a specific infectious agent or combination of infectious agents across different animal species, particularly human patients and pet dogs and cats that share the same environment and potentially similar vector exposures, might provide useful indicators of chronic infectious disease causation. This is an important concept with respect to the mounting importance of the global One Health paradigm that proposes much closer integration of human and veterinary medicine (Jones et al. 2008; Taylor et al. 2001). It is essential that cross-species infectious agents are investigated in a collaborative fashion

by integrated teams of environmental, medical, and veterinary medical researchers and public health officials and that appropriate resources are allocated to permit this One Health translational research approach to comparative infectious disease causation to be successful. For zoonotic pathogens shared between animals and man, a coordinated One Health approach to investigation and application of the proposed fifth Koch's postulate might prove beneficial for animal health and human health.

Isolation and Molecular Detection of *Bartonella* Species

Because conventional microbiological techniques lack sensitivity, bartonellosis is usually diagnosed by PCR amplification of organism-specific DNA sequences and/or through serological testing. Recently, the development of a more sensitive isolation approach using insect cell culture-based growth medium such as BAPGM followed by PCR amplification and DNA sequencing has greatly facilitated the molecular detection or successful isolation of *Bartonella* spp. from the blood of sick or healthy animals, including cats, dogs, dolphins, horses, and humans (Duncan et al. 2007; Lynch et al. 2011; Riess et al. 2008). Most important, the use of this enrichment growth medium before PCR testing has allowed our research group to confirm that nonimmunocompromised human patients, often including veterinarians and veterinary technicians, can have chronic intravascular infections with *Bartonella* spp. that span months to years.

It is increasingly clear that no currently available, single diagnostic strategy will confirm infection with a *Bartonella* sp. in all immunocompetent patients. Recent reports have identified an intraendothelial, as well as intraerythrocytic, localization for these bacteria, which represents a unique strategy for bacterial persistence. Until the development, optimization, and validation of insect cell culture medium approaches, the diagnostic detection of a *Bartonella* spp. in sick dogs, horses, or human patient samples was very insensitive. In fact, persistent bacteremia with *B. henselae* was not thought to occur whatsoever in immunocompetent human beings. As described herein, studies from our laboratory have documented persistent infection with *B. henselae*, *B. koehlerae*, and *B. vinsonii* subsp *berkhoffii* in nonimmuncompromised human patients. In one study, seroreactivity was found in only 30.4% of the patients in which *Bartonella* sp. infection was confirmed by PCR and DNA sequencing (Maggi et al. 2011). Therefore, Bartonella serology lacks sensitivity and can only be used to implicate prior exposure to a *Bartonella* sp. Even when serum from CSD patients, which is caused by *B. henselae,* is used in various diagnostic laboratories for immunofluorescent antibody testing, test sensitivities have ranged 14–100% (Sander et al. 1998; Tsuruoka et al. 2012). For the diagnostic evaluation of future animal and human patients, a panel consisting of multiple *Bartonella* spp. for serological assays, in conjunction with enrichment culture/PCR from blood, serum, tissues or cerebrospinal fluid, will enhance the diagnostic sensitivity and specificity needed to achieve a diagnosis of bartonellosis.

Current Trends In Bartonella Research

There are substantial, ongoing efforts to better delineate the pathogenic mechanisms by which *Bartonella* spp. induce disease, particularly in the context of inducing vasoproliferative vascular lesions. Recent reviews have summarized current knowledge of *Bartonella* pathogenesis (Ben-Tekaya et al. 2013; Harms and Dehio 2012; Kaiser et al. 2011). Despite ongoing research efforts to better understand the pathogenesis of *Bartonella* sp. infections, numerous questions remain to be answered.

Establishing the molecular and biochemical pathogenesis of *Bartonella*-induced vasoproliferation has been a major focus for *Bartonella* researchers. A substantial body of literature now supports the ability of *B. henselae*, *B. quintana*, *B. bacilliformis*, and *B. vinsonii* subsp. *berkhoffii* to induce the production of VEGF and resultant vasoproliferation of endothelial cells (Beerlage et al. 2012; Harms and Dehio 2012; Kaiser et al. 2011). In the context of naturally occurring cancers, increased expression of VEGF has been documented in association with several vascular tumors, including hemangiosarcoma in dogs, epithelioid hemangioendothelioma (EHE), in human patients and hemangiopericytoma in dogs (Varanat et al. 2011). Although causation has not been established, *B. vinsonii* subsp. *berkhoffii* genotype II was isolated from a boy with an EHE and from a dog with a hemangiopericytoma (Breitschwerdt et al. 2009). Subsequently, infection with *B. henselae* and *B. koehlerae* was documented in EHE patients from Australia and England (Mascarelli et al. 2011) and DNA of *B. henselae*, *B. vinsonii* subp. *berkhoffii*, or both organisms was amplified and sequenced from hemangiopericytomas in dogs, a horse, and a red wolf (Beerlage et al. 2012). Thus, on a comparative medical or One Health basis, intravascular infection with one or more *Bartonella* species has been documented in EHE patients from three continents and in hemangiopericytomas from three animal species, suggesting that persistent intravascular infection with these bacteria might contribute to the development of these highly unusual and relatively uncommon vascular tumors in nonimmunocompromised people and in animals, respectively. Also, on a comparative microbiological and pathological basis, *B. henselae*, *B. koehlerae*, or *B. vinsonii* subsp. *berkhoffii* DNA has recently been amplified and sequenced from formalin-fixed and paraffin wax–embedded tissues from cats and a steer with systemic reactive angiomatosis (Beerlage et al. 2012). This rare disease is characterized pathologically by the proliferation of vessels throughout numerous tissues within the animal's body. Collectively, the above comparative microbiological and pathological findings served as the basis for a retrospective study designed to determine whether *Bartonella* spp. might play a role in the pathogenesis of canine hemangiosarcoma (a malignant tumor of vascular endothelial cells that generally arises in either the spleen

or the right atrium of the heart), one of the most common cancers affecting dogs (Varanat et al. 2011). Using surgically obtained formalin-fixed and paraffin wax–embedded tissue biopsy samples from 50 dogs with splenic hemangiosarcoma, a statistically higher prevalence of *Bartonella* sp. DNA (26%) was found, as compared with hemotropic *Mycoplasma* sp. DNA (2%) or *Babesia* sp. DNA (6%). In addition, *Bartonella* sp. DNA was statistically more prevalent in the spleens of dogs with hemangiosarcoma (26%), as compared with the spleens from dogs with lymphoid nodular hyperplasia (10%). Although causation cannot be established by a geographically limited study, the comparative pathological evidence outlined above implicates a potential role for *Bartonella* spp. in nonimmunocompromised animals and people, including EHE in human patients, hemangiopericytoma and hemangiosarcoma in dogs, and systemic reactive angiomatosis in cats. If the association between infection with a *Bartonella* spp. and canine hemangiosarcoma is confirmed as causal, the development of a vaccine to prevent *Bartonella* sp. infections might decrease or eliminate one of the more common, serious, and potentially life-threatening malignancies affecting dogs, analogous to the papillomavirus vaccine that was recently introduced to decrease the prevalence of cervical cancer in woman.

A second area of *Bartonella* sp. research emphasis is the identification of bacterial virulence factors. Based upon clinical and epidemiological evidence, strains of a *Bartonella* sp. vary in their virulence. For example, after flea transmission, highly pathogenic strains of *B. henselae*, for which the cat is the primary reservoir, can induce granulomatous myocarditis in young cats (Varanat et al. 2012). Until recently, mechanisms that facilitate persistent *Bartonella* bacteremia in mammals were not well understood. Nonhemolytic intracellular colonization of erythrocytes in conjunction with the ability to invade and replicate within endothelial cells would preserve the organisms for efficient vector transmission, protect *Bartonella* from the host immune response, and potentially contribute to decreased antimicrobial efficacy (Chomel et al. 2006; Minnick and Battisti 2009). Although the clinical implications are not yet understood, other in vitro studies indicate that *Bartonella* spp. can infect dendritic cells, microglial cells, monocytes, and $CD34^+$ bone marrow progenitor cells. *B. vinsonii* subsp. *berkhoffii*, *B. henselae*, and other *Bartonella* spp. have developed survival mechanisms that allow for successful infection of the host and low-level intravascular and intracellular persistence in the host so that the organism is available for subsequent transmission to another vector and host. These mechanisms involve interactions with both nucleated and non-nucleated host cells and are dependent on a number of virulence factors. Studies from Christoph Dehio's research group have shown that a laterally acquired type IV secretion system (T4SS; Trw) diversified among the *Bartonella* lineages to facilitate host-restricted adhesion to erythrocytes in a wide range of mammals (Harms and Dehio 2012). Other studies have shown that *Bartonella* spp. may establish infection internal to red blood cells in a species-specific manner, but the ability to invade other cell types does not appear to be as restrictive (Harms and Dehio 2012; Houchaima et al. 2013). This is important because *Bartonella* spp. are able to hide in one or more protected host niche(s) and slowly infect red blood cells over time to facilitate a persistent or relapsing intravascular infection within the host. The location of the protected host niche(s) remains a major clinically relevant question and has created some controversy among *Bartonella* researchers.

Other characterized virulence factors are briefly highlighted herein. Apart from the initial adherence and invasion, these virulence factors collectively contribute to the pathogenesis of *Bartonella* infections by modulating the immune response to allow persistence, by forming new blood vessels through endothelial cell proliferation, and by potentially influencing other as yet to be determined host cell functions.

T4SSs (VirB/D4, Vbh types) represent an elegant assembly of molecules that facilitates the efficient transfer of bacterial effector molecules to the host cell by acting as a translocation pore (Houchaima et al. 2013). Once translocated to the host cell, these *Bartonella* effector proteins alter several host cell functions to the ultimate benefit of the bacteria. These *Bartonella* effector proteins promote invasome formation, allow for entry of *Bartonella* into the host cell, promote angiogenesis, and inhibit apoptosis of the infected host cell (Franz and Kempf 2011). Certain *Bartonella* species within lineage 4 (including *B. quintana, B. henselae*, and *B. vinsonii* subspecies *berkhoffii*) also have a Trw T4SS that is critical for bacterial adherence to red blood cells and determines host specificity (Harms and Dehio 2012; Houchaima et al. 2013; Vayssier-Taussat et al. 2010). Much energy is required by the bacteria to form the translocation pore, thus a transcriptional regulatory system exerts control over the process. In *Bartonella* spp., the VirB T4SS is tightly regulated by the combination of a histidine kinase and a response regulator, known as the BatR/BatS two-component regulatory system (Houchaima et al. 2013). Flagella are present in *Bartonella* spp. from lineages 1 to 3, but not lineage 4 (Houchaima et al. 2013). As a virulence factor, flagella appear to be important in penetration of red blood cells and, potentially, attachment of the bacteria to the host cell. In addition, as studied in Volkhard Kempf's laboratory, trimeric autotransporter adhesins facilitate binding to host cell proteins. *Bartonella* adhesin A (BadA) is a well-known *B. henselae* surface protein that confers bacterial autoagglutination properties, allowing for adhesion to host cells and the extracellular matrix, and inhibits endothelial cell apoptosis as well as induces angiogenesis (Franz and Kempf 2011; Riess et al. 2007). As studied in Dr. Jane Koehler's laboratory, variably expressed outer membrane proteins from *B. quintana* also promote adhesion (through hyaluronate and vitronectin in extra cellular matrix) and facilitate angiogenesis (Minnick and Battisti 2009; Zhang et al. 2004). Lipopolysaccharide (LPS), a component of the cell wall of most Gram-negative bacteria, from *B. bacilliformis*, *B. henselae*, and *B. quintana* does not activate a mammalian humoral response (Harms and Dehio 2012). Furthermore, LPS from *Bartonella quintana* affects the host immune response by remaining undetectable

by Toll-like receptor 4, which, when activated by LPS from other Gram-negative bacteria, results in a strong inflammatory response (Harms and Dehio 2012). *Bartonella* sp. LPS has been shown to have potent anti-inflammatory properties under certain circumstances and proinflammatory properties under other conditions. Based upon limited case data (Breitschwerdt et al. 2012), *Bartonella* spp. can be isolated from the cerebrospinal fluid of patients with minimal pathological evidence (i.e., increased protein and cell counts) to support inflammation or infection, perhaps due in part to the anti-inflammatory properties of *Bartonella* sp. LPS.

Because of persistent intravascular and intracellular infection, *Bartonella* sp. infections have been associated with the presence of antinuclear antibodies in dogs (Smith et al. 2004) and antineutrophil cytoplasmic antibodies in both dogs (Karagianni et al. 2012) and human patients (Satake et al. 2011). The extent to which chronic intravascular or endotheliotropic infection contributes to immune-mediated or autoimmune (molecular mimicry) phenomena in bartonellosis patients remains unclear but deserves additional research consideration.

Future Needs in *Bartonella* Research

The field of *Bartonella* research remains in its infancy and is rich in questions, for which patient-relevant answers are badly needed. Based upon the evolving understanding of the medical importance of this genus of bacteria, basic and translational research initiatives have the potential to generate substantial benefits for animal and human health as answers to current questions are found. Based upon recent One Health observations, it is possible that directed *Bartonella* research could substantially reduce animal and human suffering associated with chronic debilitating disease processes. In addition, the resulting outcomes could include substantial financial healthcare savings for patients, insurance companies, and society. Some opportunities for translational research lie in developing more sensitive diagnostic assays for *Bartonella* spp. Diagnostic assays that provide species-level identification in a multiplex format would be most beneficial. Also, further improvements in culture sensitivity are needed and could be made by further defining optimal growth conditions for *Bartonella* clinical isolates, including length of time for culture, and by establishing the optimal frequency of patient blood draws, as indicated by one recent study (Pultorak et al. 2013). Another challenge to researchers is to develop serological assays that better balance sensitivity and specificity for various *Bartonella* species by using paired or sequentially collected serum samples to clearly understand the kinetics of antibody production in animal and human patients. Additional characterization of virulence factors and demonstration of their contribution to pathogenesis, as well as how members of this genus maintain persistence in the host, will further our understanding of the pathogenesis of *Bartonella* infections. There is also a critical need for research to elucidate the mechanism(s) by which chronic interplay between the host's immune response and the bacteria ultimately leads to disease manifestations. Perhaps even more daunting, but nevertheless critical, is to plan prospective case–control clinical studies that can provide strong evidence of cause–effect relationship (rather than disease association only) for nonspecific symptoms, as well as specific disease manifestations that can be induced by chronic *Bartonella* bloodstream infections in animals and humans. Studies are specifically needed to address the potential role of *Bartonella* spp. in a spectrum of human vascular, rheumatologic, and neurologic diseases (Breitschwerdt et al. 2012; Maggi et al. 2012). As a specific example, the mechanisms by which some *B. henselae* strains cause aphasia, encephalopathy, neuropathy, seizures, or transverse myelitis should be studied. From a clinical perspective, efforts to standardize antibiotic dose and duration of treatment regimens, based upon both in vitro antibiotic susceptibility testing and patient outcome assessments are critically needed to effectively manage patients with bartonellosis. In addition, research is needed to determine whether antibiotic resistance or other factors contribute to treatment failures recently documented in some bartonellosis patients. From a One Health perspective, safe and efficacious vaccines could prevent infection in pets and thereby help to prevent infection in people.

As important, emerging, zoonotic pathogens, *Bartonella* spp. provide a perfect opportunity to reinforce the One Health concept (i.e., the need to integrate animal health, human health, and environmental factors) while coordinating research priorities designed to enhance diagnosis, treatment, and prevention of *Bartonella* spp. infections. A better understanding of the interactions of people, vectors, animals, and the environment will allow for improvements in epidemiologic and medical knowledge of the myriad disease manifestations and clinical presentations collectively known as bartonellosis.

Concluding Thoughts

During medical school, physicians, veterinarians, and other animal health professionals should be educated as to the large number of *Bartonella* spp. in nature, the extensive spectrum of animal reservoir hosts, the diversity of confirmed and potential arthropod vectors, current limitations associated with diagnosis and establishment of treatment efficacy, and the ecological and evolving medical complexity associated with these highly evolved, intravascular, endotheliotropic bacteria. It is critical for clinicians (physicians and veterinarians) to consider each patient's travel history, exposures to domestic animals and wildlife, exposure to arthropod or insect vectors, and potentially whether there is a history of blood product administration. Biologists, ecologists, vector biologists, and other environmental scientists should further define the ecology, biology, and vector competence for various *Bartonella* spp. in nature so as to better direct the development of practical prevention strategies.

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