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Lynn Guptill

► **To cite this version:**

Lynn Guptill. Bartonellosis. Veterinary Microbiology, 2010, 140 (3-4), pp.347.
10.1016/j.vetmic.2009.11.011 . hal-00556059

HAL Id: hal-00556059

<https://hal.science/hal-00556059>

Submitted on 15 Jan 2011

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Accepted Manuscript

Title: Bartonellosis

Author: Lynn Guptill

PII: S0378-1135(09)00560-4
DOI: doi:10.1016/j.vetmic.2009.11.011
Reference: VETMIC 4666

To appear in: *VETMIC*

Received date: 29-6-2009
Revised date: 6-11-2009
Accepted date: 10-11-2009



Please cite this article as: Guptill, L., Bartonellosis, *Veterinary Microbiology* (2008), doi:10.1016/j.vetmic.2009.11.011

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Bartonellosis

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1 Abstract

2 Bartonellosis is a constellation of clinical conditions affecting human beings and a variety
3 of animals. Many *Bartonella* infections are zoonotic, with some of the most commonly reported
4 zoonotic manifestations of infection including cat scratch disease, bacillary angiomatosis,
5 endocarditis, and neuroretinitis. Companion animals serve as reservoirs for several zoonotic
6 species of *Bartonella*, and may also serve as sentinels for zoonotic *Bartonella* species harbored
7 by wildlife.

8 This article provides an overview of bartonellosis of dogs and cats, and discusses the public
9 health implications of animal bartonellosis.

10

11 **Keywords:** *Bartonella*, bartonellosis, cat, dog, zoonosis

12

13 INTRODUCTION

14 *Bartonella* spp. are small, vector-transmitted Gram-negative bacteria. Since the early
15 1990s many *Bartonella* species have been described, and there are now over 22 named species of
16 *Bartonella*, including species that originally comprised the genera *Rochalimaea* and *Grahamella*
17 (Brenner et al., 1993). The *Bartonellas* are phylogenetically close to the *Rickettsiae* and bacteria
18 of the species *Brucella*, *Agrobacterium*, and *Afipia* (Birtles et al., 1995; Brenner et al., 1993;
19 Weisburg et al., 1985). These relationships have provided some insights into the pathogenesis
20 and natural history of *Bartonella* infections.

21 The first *Bartonella* species described was *B. bacilliformis*, named for Peruvian
22 microbiologist Alberto Barton, and endemic to South America. Human bartonellosis caused by
23 *B. bacilliformis* (not considered zoonotic) is transmitted by sandflies and consists of two clinical

24 conditions; a devastating hemolytic anemia, Oroya fever or Carrión's disease, and verruga
25 peruana or Peruvian wart, a systemic disorder with verrucous cutaneous lesions that result from
26 endothelial cell proliferation. Carrión's disease is named for Peruvian medical student Daniel
27 Carrión, who in 1885 inoculated himself with material from a cutaneous lesion of verruga
28 peruana, documented his ensuing illness, demonstrating the relationship between the two
29 conditions, and sadly, succumbed to the disease.

30 The role of *Bartonella* species as pathogens of human beings and domestic animals is the
31 subject of much ongoing investigation. Establishing true causal associations of *Bartonella*
32 infections with clinical disease has been challenging in many instances. Current investigations are
33 helping to better define the potential virulence factors of some *Bartonella* species, and to contribute
34 to an understanding of the pathogenesis of *Bartonella* infections. This paper focuses on
35 bartonellosis of dogs and cats, and discusses public health implications of animal bartonellosis.

36 ETIOLOGY AND EPIDEMIOLOGY

37 *Bartonella* species have a worldwide distribution with highest prevalences in areas where
38 conditions are most favorable for arthropod vectors. Feline *B. henselae* infection was first
39 reported in 1992 (Regnery et al, 1992), and canine *B. vinsonii* subsp. *berkhoffii* infection in 1994
40 (Breitschwerdt et al, 1995). Reports of *Bartonella* infections in many other animal species have
41 followed. High prevalences are reported for *B. henselae* in cats (up to 93 percent seroprevalence
42 in some cat colonies), *B. bovis* and *B. chomelii* in cattle (42 to 89% prevalence), *B. vinsonii*
43 subsp. *berkhoffii* in coyotes (35-71% seroprevalence), *B. vinsonii* subsp. *berkhoffii* in dogs (1-
44 38% seroprevalence) and *B. henselae* in dogs (10-35% seroprevalence) (Chang et al, 2000a;
45 Chang et al, 2000b; Jameson et al, 1995; Cherry et al, 2009; Nutter et al, 2004; Solano-Gallego
46 et al, 2004; Henn et al, 2005; Suksawat et al, 2001; Maillard et al, 2006). Seroprevalences are

47 higher in older cats than in younger animals, whereas prevalence of bacteremia is higher in
48 younger animals (Chang et al, 2000a; Maillard et al, 2006; Chomel et al, 1995).

49 Many *Bartonella* species appear to be well-adapted to extended survival in mammalian
50 reservoir hosts. Prolonged bacteremia in clinically normal reservoir hosts is considered common
51 (Chomel et al., 2003a; Chomel et al., 2009a; Jacomo et al., 2002). Cats appear to be the primary
52 mammalian reservoir for the important zoonotic species, *B. henselae*, and also for *B.*
53 *clarridgeiae* and possibly *B. koehlerae* (Chomel et al., 2004). Coyotes and dogs may be
54 mammalian reservoirs for *B. vinsonii* subsp. *berkhoffii* and dogs and foxes for *candidatus B.*
55 *rochalimae* (Henn et al, 2009; Chomel et al 2003a). Other examples of reservoir hosts include
56 cattle, which appear to be the mammalian reservoir for *B. bovis*, California ground squirrels for
57 *candidatus B. washoensis*, and human beings for *B. quintana* and *B. bacilliformis* (Bermond et
58 al., 2002; Kosoy et al., 2003). The mechanisms that support persistent *Bartonella* bacteremia in
59 mammals are being investigated. Location within erythrocytes and vascular endothelial cells is
60 believed to protect *Bartonellas* from antimicrobial agents (Rolain et al., 2003c). Immune system
61 avoidance via intracellular location, frequent genetic rearrangements, and alteration of outer
62 membrane proteins, is also considered important (Berghoff et al., 2007; Chomel et al., 2003a;
63 Chomel et al., 2009a; Jacomo et al., 2002; Mandle et al., 2005; Seubert et al., 2002). Genetically
64 diverse strains of *B. henselae* and of *B. vinsonii* subsp. *berkhoffii* are described (Maggi et al.,
65 2006). For example, there are two recognized 16S rRNA types of *B. henselae* and there are
66 subgroups within each type (Maruyama et al., 2001; Zeaiter et al., 2002). Other molecular
67 methods also demonstrate remarkable diversity among *B. henselae* isolates, (Berghoff et al., 2007;
68 Dillon et al., 2002; Iredell et al., 2003; Kyme et al., 2003; Li et al., 2006; Maruyama et al., 2000;
69 Iredell et al., 2002; Monteil et al., 2007). There is evidence of genomic variation in *B. henselae*

70 during the course of infection in cats (Berghoff et al., 2007; Kabeya et al., 2002). Such variation
71 likely enhances the ability of *B. henselae* to persist in infected cats for prolonged periods, and may
72 be useful in furthering the understanding of the pathogenicity of various *B. henselae* isolates
73 (Arvand et al., 2001; Arvand et al., 2007).

74 Infection of a single host animal with more than one *Bartonella* species is reported in cats,
75 dogs, cattle, and species of wild mammals, including rodents (Cherry et al., 2009; Diniz et al., 2007;
76 Gurfield et al., 1997; Telfer et al., 2007). Additionally, co-infection with multiple genetic types of
77 *B. henselae* or *B. vinsonii* subspecies *berkhoffii* is reported for cats and dogs, respectively
78 (Duncan et al., 2007a; Gurfield et al., 1997). Regional differences in prevalence of infection of
79 cats with different rRNA types of *B. henselae* are reported (Bergmans et al., 1997; Guptill et al.,
80 2004; Gurfield et al., 2001; Heller et al., 1997).

81 At least fourteen *Bartonella* species or candidate species are considered zoonotic or
82 potentially zoonotic. Of the zoonotic species, several may be transmitted to human beings via
83 companion animals, including *B. henselae* (cats, possibly dogs), *B. vinsonii* subsp. *berkhoffii* (dogs),
84 and *B. koehlerae* (possibly cats). *Bartonella clarridgeiae* and *candidatus B. rochalimae* are
85 considered potentially zoonotic, with transmission potentially via cats (*B. clarridgeiae*) or dogs
86 (potentially both species) (Avidor et al., 2004; Chomel et al., 2004; Chomel et al., 2009b). Whether
87 *B. clarridgeiae* has truly been associated with human disease is still debated. *Bartonella quintana*
88 has long been understood to be a human pathogen with human beings as the reservoir host, and has
89 not previously been considered zoonotic. However, recent reports have noted the presence of *B.*
90 *quintana* in cats and dogs, and one report suggested transmission of *B. quintana* from companion
91 animals to human beings (Breitschwerdt et al., 2007; La et al., 2005; Kelly et al., 2006). *Candidatus*

92 *B. rochalimae* may be zoonotic with foxes and dogs as possible reservoir hosts (Chomel et al.,
93 2009b).

94 More is known about *B. henselae* than is known for any of the other zoonotic *Bartonella*
95 species, and *B. henselae* may be the *Bartonella* species most commonly zoonotic. The
96 epidemiology of *Bartonella* infections in companion animals, wild animals, and human beings is
97 still being clarified. It is possible that species of *Bartonella* not previously considered a zoonotic
98 threat may also be transmitted to human beings from animals. New information about existing
99 *Bartonella* species, and the frequent addition of new *Bartonella* species to our knowledge base,
100 makes it challenging to remain up-to-date regarding the many possible forms and sources of
101 bartonellosis in animals and in human beings. For example, a recent publication reported that
102 *Bartonella* DNA of 4 species considered zoonotic or potentially zoonotic (*B. grahamii*, *B.*
103 *elizabethae*, *B. washoensis*, *B. clarridgeiae*) was detected in some exotic animals imported into
104 Japan as pets (Inoue et al., 2009).

105 TRANSMISSION AND PATHOGENESIS

106 *Bartonella henselae* is naturally transmitted among cats by cat fleas (*Ctenocephalides*
107 *felis felis*). Chronic recurring bacteremia is common in infected cats, and likely facilitates vector
108 transmission, similar to what is documented for other pathogens that are transmitted by
109 hematophagous arthropod vectors (Barbour and Restrepo, 2000; Breitschwerdt and Kordick,
110 2000; Schulein et al., 2001). *B. henselae* was experimentally transmitted among cats by
111 transferring fleas fed on naturally infected cats to specific pathogen free (SPF) cats, and by
112 intradermal (ID) inoculation of excrement collected from fleas fed on *B. henselae*-infected cats
113 (Chomel et al., 1996; Finkelstein et al., 2002; Foil et al., 1999). Transmission via flea saliva has
114 not been documented (Foil et al., 1999). Cats were also experimentally infected with *B. henselae*

115 and *B. clarridgeiae* through IV or IM inoculation with infected cat blood, and *B. henselae* was
116 transmitted by intravenous, subcutaneous, ID, or oral routes of inoculation with plate-grown
117 bacteria (Abbott et al., 1997; Guptill et al., 1997; Guptill et al., 1999; Kordick et al., 1999;
118 Kordick and Breitschwerdt, 1997; Mikolajczyk and O'Reilly, 2000; O'Reilly et al., 1999).
119 *Bartonella henselae* transmission has not occurred when infected cats cohabit with uninfected
120 cats in a flea-free environment, indicating that transmission among cats does not occur through
121 cat bites, scratches, grooming, or sharing of food dishes and litter boxes. In addition, there was
122 no transmission between bacteremic female cats and uninfected males during mating, or to the
123 kittens of infected females either during gestation or in the neonatal period, also in flea-free
124 environments (Abbott et al., 1997; Guptill et al., 1997; Guptill et al., 1998).

125 Ticks have been proposed as vectors for transmission of *Bartonella* species among cats,
126 human beings, dogs, and other mammalian hosts (Bergmans, 1996; Cotté et al., 2008;
127 Pappalardo et al., 1997; Slater et al., 1990; Welch et al., 1999). *Bartonella henselae* and other
128 *Bartonella* spp. were detected by PCR in questing ticks (Chang et al., 2002b; Chang et al., 2001;
129 Sanogo et al., 2003). Transtadial transmission of *B. henselae* was recently demonstrated in *Ixodes*
130 *ricinus* ticks and these ticks are likely competent vectors for *B. henselae* (Cotté et al., 2008). Deer
131 keds likely transmit *B. schoenbuchensis*, and human body lice transmit *B. quintana* (Dehio et al.,
132 2004; Raoult and Roux, 1999; Reeves et al., 2006). *Bartonella* species have been detected in
133 other biting flies, and in many species of fleas and ticks in addition to those already noted
134 (Chomel et al., 2009a; Marié et al., 2006; Parola et al., 2002; Rolain et al., 2003a).

135 **Virulence factors of *Bartonella* species**

136 A comprehensive review of virulence factors of *Bartonella* species is beyond the scope of
137 this paper. Investigation of potential virulence factors for most *Bartonella* species is ongoing in

138 several laboratories; the reader is referred to a recent comprehensive review of *Bartonella*
139 virulence factors and persistence mechanisms for detailed information (Minnick and Battisti,
140 2009). Virulence factors characterized in several *Bartonella* species include adhesins, heme
141 acquisition/utilization mechanisms, type IV secretion systems (T4SS), and a low-potency
142 lipopolysaccharide (LPS), among others (Minnick and Battisti, 2009). Interestingly, purified
143 LPS of *B. quintana* was recently shown to inhibit inflammatory changes in a mouse model of
144 immune-mediated arthritis via inhibition of TLR-4 activation (Abdollahi-Roodsaz et al., 2007).
145 Type IV secretion systems, while not identified in the type species *B. bacilliformis*, are important
146 virulence factors for other *Bartonella* species. The T4SS trw has been identified in *B. henselae*,
147 *B. quintana*, *B. birtlesii*, *B. grahamii*, and *B. tribocorum*, and is believed important in erythrocyte
148 and endothelial cell invasion (Minnick and Battisti, 2009; Dehio, 2008). The VirB/Vir D4 T4SS,
149 investigated in *B. tribocorum* and *B. henselae*, among others, has important effects including
150 activation of nuclear factor kappa B (NF- κ B), leading to release of pro-inflammatory or pro-
151 angiogenic cytokines, and inhibition of apoptosis of colonized endothelial cells (Dehio, 2008;
152 Minnick and Battisti, 2009). Further investigation of virulence and persistence mechanisms of
153 the *Bartonella* species will advance our understanding of the remarkable ability of these
154 organisms to persist in vertebrate hosts for prolonged periods.

155 **Relapsing bacteremia and immune protection**

156 Experimentally infected cats maintained relapsing *B. henselae* or *B. clarridgeiae*
157 bacteremia for as long as 454 days (Kordick et al., 1999). Relapsing bacteremia reported in
158 some naturally infected cats appeared to result from reinfection via fleas, indicating a lack of
159 immune protection following *Bartonella* infection (Arvand et al., 2008; Kordick et al., 1995).

160 Experimentally infected cats became immune to challenge infection with homologous
161 strains of *Bartonella*, but there was a lack of protection against re-infection with heterologous
162 *Bartonella* isolates (Greene et al, 1996; Yamamoto et al., 1997). The level of bacteremia and
163 degree of susceptibility to reinfection following challenge inoculation varied with the strain and
164 species of *Bartonella*. Cats infected with *B. henselae* 16S rRNA type I or II were susceptible to
165 challenge infection with *B. clarridgeiae*, and cats infected with *B. koehlerae* or *B. clarridgeiae*
166 were susceptible to challenge infection with *B. henselae* 16s rRNA type I or type II. Cats
167 previously infected with *B. henselae* 16S rRNA type II were resistant to re-infection with the
168 same *B. henselae* strain, but were susceptible to infection with *B. henselae* 16S rRNA type I
169 (Yamamoto et al., 1997). In contrast, cats infected with *B. henselae* 16S rRNA type I were, as
170 expected, protected from re-infection with the same strain, but were also partially or completely
171 protected against challenge infection with a *B. henselae* 16S rRNA type II isolate (Yamamoto et
172 al., 2003). The lack of or incomplete cross-protection among *Bartonella* isolates, likely due to
173 genetic variation, has made vaccine development difficult.

174 Relapsing bacteremia is also described in rats infected with *B. tribocorum*, and relapsing
175 illness in human beings is reported in conjunction with infection with several *Bartonella* species
176 (Dehio, 2001; Maguiña et al., 2009; Schülein et al., 2001). Relapsing bacteremia may be
177 facilitated by antigenic variation, or by localization to so-called “privileged” sites such as within
178 erythrocytes or other host cells, as has been demonstrated for *B. tribocorum* and other *Bartonella*
179 species.

180 The exact localization of *Bartonella* species in mammalian hosts has not been completely
181 determined, and may differ among *Bartonella*-host pairs. Evidence indicates that individual
182 *Bartonella* species have been associated with reservoir hosts for hundreds to thousands of years,

183 and this long period of “co-evolution” has likely led to numerous means of immune evasion and
184 prolonged coexistence of *Bartonella* spp. and various reservoir hosts (Drancourt et al., 2005; La
185 et al., 2004). *Bartonella* sp. other than *B. bacilliformis* have been detected within erythrocytes of
186 naturally infected cats and human beings (Mehock et al., 1998; Rolain et al., 2002). *Bartonella*
187 may also localize and persist within vascular endothelial cells, as suggested by an in vivo model
188 of *B. tribocorum* infection of rats (Dehio, 2001). Studies in a rat model of *B. tribocorum*
189 infection suggest that *Bartonella* may, following initial inoculation, colonize vascular endothelial
190 cells as a primary niche. In this rat model, *Bartonella* were shown to periodically
191 (approximately every 5 days) leave a primary niche and invade circulating erythrocytes, in which
192 protected environment they then remained for the normal lifespan of the erythrocytes (Schüle
193 et al., 2001). The details of host/pathogen interactions in other *Bartonella*/reservoir host pairs
194 have not yet been reported.

195 CLINICAL FINDINGS IN CATS AND DOGS

196 **Cats.** Existing data indicate that few cats naturally infected with *Bartonella* have notable
197 clinical signs. Given the long association of *Bartonella* and domestic cats, there have likely been
198 adaptations of the host and parasite to facilitate co-existence and minimize pathogenic effects on
199 the mammalian host. Occurrence and severity of clinical signs likely varies with the strain of
200 *Bartonella* infecting the cat (Mikolajczyk and O'Reilly, 2000; O'Reilly et al., 1999). Naturally
201 infected cats may have mild clinical signs that owners do not observe. Some naturally infected
202 cats developed fever following elective surgical procedures (Breitschwerdt, 1997). Uveitis may
203 be another manifestation of natural *Bartonella* infection (Lappin and Black, 1999). *Bartonella*
204 *henselae* type I was associated with fatal blood culture-negative vegetative aortic valve
205 endocarditis in two naturally infected cats (Chomel et al., 2003c; Chomel et al., 2009c). Whether

206 *Bartonella* spp. are present in lymph nodes of some cats with persistent lymphadenomegaly or some
207 cases of peliosis hepatis in cats is unknown (Brown et al., 1994; Kirkpatrick et al., 1989).

208 The majority of information regarding clinical signs is available from experimental studies
209 in which cats were infected with *B. henselae*. A few cats were experimentally infected with *B.*
210 *clarridgeiae* and *B. henselae* together, and clinical findings in these cats paralleled those reported
211 for cats infected with *B. henselae* alone. Cats experimentally infected with *B. koehlerae* or *B.*
212 *rochalimae* exhibited no clinical signs (Chomel et al., 2009b; Yamamoto et al., 2002).

213 Clinical signs in cats experimentally infected with *B. henselae* were usually mild though
214 varied with the strain of *B. henselae* used for inoculation. Cats inoculated intradermally
215 developed areas of induration or abscesses at inoculation sites, between approximately 2 days
216 and 3 to 4 weeks after inoculation, from some of which pure cultures of *B. henselae* were
217 obtained (Greene et al., 1996; Guptill et al., 1997; Kordick et al., 1999; Mikolajczyk and
218 O'Reilly, 2000; O'Reilly et al., 1999). Other transient clinical findings in many experimentally
219 infected cats included generalized or localized peripheral lymphadenomegaly (lasting for about 6
220 weeks following inoculation), and short periods of fever ($>39.4^{\circ}\text{C}$ [103°F]) during the first 48 to
221 96 hours following inoculation and again at approximately 2 weeks following inoculation. There
222 were instances of mild neurologic signs (nystagmus, whole body tremors, mild focal motor
223 seizures, either decreased or exaggerated responses to external stimuli, behavior changes), and
224 epaxial muscle pain in a few cats. Some cats were lethargic and anorexic during febrile periods
225 (Guptill et al., 1997; Kordick et al., 1999; Kordick and Breitschwerdt, 1997; Mikolajczyk and
226 O'Reilly, 2000; O'Reilly et al., 1999). Reproductive failure occurred in some cats experimentally
227 infected via intradermal inoculation with *B. henselae* (Guptill et al., 1998; Abbott et al., 1997).

228 Some cats infected via fleas exhibited no clinical signs while in one study two cats developed
229 cardiac disease (Bradbury and Lappin, 2009; Chomel et al., 1996).

230 A potential causative role of *Bartonella* spp. in chronic diseases of cats has been
231 proposed because *Bartonella* bacteremia is common and prolonged. For example, results of a
232 study in Japan suggested that cats seropositive for both *B. henselae* and feline immunodeficiency
233 virus were more likely to have gingivitis or lymphadenomegaly than cats seropositive for either
234 agent alone (Ueno et al., 1996). Results of a Swiss study suggested possible associations
235 between *B. henselae* seropositivity and stomatitis or unspecified urinary tract disorders (Glaus et
236 al., 1997). However, because of the high prevalence of *Bartonella* exposure in the domestic cat
237 population, extensive, carefully controlled epidemiologic investigations are needed to determine
238 whether particular clinical conditions are truly associated with *B. henselae* infections in cats.

239 Some small epidemiologic studies have evaluated the association between *Bartonella* exposure
240 and clinical conditions such as some neurologic conditions, stomatitis, uveitis, and fever. To
241 date, there has not been statistically significant association of documented active *Bartonella*
242 infection with the aforementioned conditions in naturally infected cats (Fontenelle et al., 2008;
243 Lappin et al., 2008; Pearce et al., 2006; Quimby et al., 2008). Clinical conditions that have been
244 proposed as attributable to feline bartonellosis may also result from other etiologies, and
245 determining in which cats *Bartonella* infection in fact causes clinical signs is difficult.

246 **Dogs:** There are case reports of dogs with varying clinical conditions from which *Bartonella*
247 DNA has been detected by polymerase chain reaction amplification of various gene fragments,
248 or less commonly, *Bartonella* has been isolated (Cross et al., 2008; Leibovitz et al., 2008; Mellor
249 et al., 2006; Saunders and Monroe, 2006). There are fewer data available for dogs than for cats
250 experimentally infected with *Bartonella*. Dogs experimentally infected with *B. vinsonii* subsp.

251 *berkhoffii* exhibited no clinical signs other than transient fever in a few dogs. Infected dogs had
252 some evidence of mild immunosuppression including either temporary cyclic decreases or mild
253 sustained decreases in peripheral blood CD8+ lymphocyte numbers (Pappalardo et al., 2000a;
254 Pappalardo et al., 2001). Two dogs experimentally infected with *B. rochalimae* exhibited no
255 clinical abnormalities other than inflammation at the inoculation site (Chomel et al., 2009b).

256 Some conditions with which *Bartonella* spp. have been associated, as a result of detection of
257 *Bartonella* in tissues of clinically ill dogs, include endocarditis (*B. vinsonii* subsp. *berkhoffii*, *B.*
258 *clarridgeiae*, *B. quintana*, *candidatus B. washoensis*, *B. rochalimae*), cardiac arrhythmias (*B.*
259 *vinsonii* subsp. *berkhoffii*), granulomatous rhinitis (*B. vinsonii* subsp. *berkhoffii*), peliosis hepatis
260 (*B. henselae*), meningoradiculoneuritis with dermatitis or panniculitis (*B. vinsonii* subsp.
261 *berkhoffii*), and granulomatous lymphadenitis (*B. henselae*) (Breitschwerdt et al., 1999; Chomel
262 et al., 2003b; Chomel et al., 2001; Cross et al., 2008; Henn et al., 2009; Kitchell et al., 2000;
263 Leibovitz et al., 2008; MacDonald et al., 2004; Mellor et al., 2006; Morales et al., 2007;
264 Pappalardo et al., 2000b). The majority of these reports involve only one or just a few dogs, with
265 endocarditis the exception. Endocarditis appears to be the clinical condition having the strongest
266 association with *Bartonella* infection in dogs, and most cases of canine endocarditis attributable
267 to *Bartonella* are caused by *B. vinsonii* subsp. *berkhoffii*. A recent study found no association
268 between *Bartonella* and chronic rhinosinusitis in dogs (Hawkins et al., 2008).

269 Whether *Bartonellae* are primary pathogens of dogs, or opportunistic pathogens, is not
270 completely clear. For dogs and cats, the potential for co-infection with other vector-transmitted
271 pathogens, and the likelihood that clinical conditions may be a result of co-infection rather than
272 attributed to one potential pathogen, must always be considered when evaluating ill animals.

273 DIAGNOSIS

274 **Cats:** The high prevalence of *Bartonella* bacteremia in cats makes establishing a causative
275 association between *Bartonella* infection and illness difficult. In addition to the potential need to
276 test for *Bartonella* infections in ill cats, veterinarians will be asked to test healthy pet cats
277 belonging to clients with *Bartonella*-related illnesses, or to screen healthy cats that are being
278 considered as pets, particularly for people considered most susceptible to *Bartonella* infections
279 (see Public Health).

280 Clinical Laboratory Findings and Pathologic Findings: Most experimentally infected cats had no
281 abnormalities on complete blood counts, serum biochemical tests, or urine analysis. Some cats
282 had transient anemia early in the course of infection, and some had persistent eosinophilia
283 (Kordick et al., 1999). Mature neutrophilia occurred in some cats, especially during periods of
284 skin inflammation (Guptill et al., 1997; Guptill et al., 1999). Acutely and chronically infected
285 cats had hyperplasia of lymphoid organs, and small foci of lymphocytic, pyogranulomatous, or
286 neutrophilic inflammation in multiple tissues (lung, liver, spleen, kidney, heart) (Guptill et al.,
287 1997; Kordick et al., 1999).

288 Finding *B. henselae* in erythrocytes of infected cats has not been an effective means of
289 detection using conventional staining methods. Confocal microscopy or special fluorescence
290 staining has been used to document intraerythrocytic location of *B. henselae*, *B. clarridgeiae* and
291 *B. koehlerae* (Mehock et al., 1998; Rolain et al., 2003b; Rolain et al., 2004).

292 Bacterial Isolation: A positive blood culture result, or culture of other tissue, is the most reliable
293 test for definitive diagnosis of active *Bartonella* infection. However, because of the relapsing
294 nature of *Bartonella* bacteremia in cats, culture is not always a sensitive diagnostic tool. Blood
295 culture is indicated for sick cats whose history and clinical presentation suggest possible
296 *Bartonella* infection, or when a client's physician requires such testing of pet cats. Blood for

297 culture should be obtained using sterile technique, and the blood placed in lysis centrifugation
298 blood culture tubes (Isolator tubes, Wampole, Cranbury, NJ) or EDTA-containing tubes. If
299 blood is collected into EDTA tubes the blood should be chilled or frozen during shipment, and
300 ideally, plastic EDTA tubes should be used. Culture of blood collected into EDTA and frozen
301 prior to culture was more sensitive than use of lysis centrifugation tubes for *Bartonella* culture
302 (Agan and Dolan, 2002; Brenner et al., 1997). Blood should be sent to laboratories familiar with
303 the culture of these fastidious organisms, and the laboratories should be contacted for specific
304 instructions regarding sample collection and submission. Special media (such as fresh chocolate
305 agar, or brain-heart infusion agar enriched with blood) and culture conditions (5% CO₂,
306 temperatures of 35 to 37 degrees Celsius), are used to enhance the likelihood of isolating
307 *Bartonella* from blood and other tissues. Extended culture times of up to 6-8 weeks are often
308 required (La Scola and Raoult, 1999).

309 Serologic Testing: Measuring serum antibodies has limited value for determining whether an ill
310 cat has an active *Bartonella* infection. Serum IgG antibodies persist in experimentally infected
311 cats for prolonged periods. How long antibodies persist following clearance of infection is not
312 known. Indirect fluorescent antibody (IFA), enzyme immunoassay (EIA), and Western blot tests
313 are available. Because of the genetic diversity of *Bartonella* organisms, infections with some
314 strains or species of *Bartonella* may be missed using any method, depending on the antigen
315 preparations used (Giladi et al., 2001; McCool et al., 2008). The positive predictive value (PPV)
316 of IFA or EIA (IgG) serologic tests for bacteremia in cats is only 39% to 46%; false positive tests
317 appear to be common. The utility of a negative serologic result is greater; false negatives are
318 uncommon and the negative predictive value of serologic tests for bacteremia or presence of
319 DNA in cat blood is high at 87% to 97% (Bergmans et al., 1997; Chomel et al., 1995; Guptill et

320 al., 2004; Gurfield et al., 2001; Lappin et al., 2008). No cut-off values allowing use of serologic
321 testing to determine whether a cat is currently infected with *Bartonella* have been established
322 (Yamamoto et al., 2003).

323 The use of Western blot tests has been advocated for serodiagnosis of feline *B. henselae*
324 infections, but the diagnostic accuracy of Western blot tests awaits further investigation. In
325 human medicine, variability in Western blot testing is still reported, and serologic responses of
326 people as evaluated by immunoblot vary (McCool et al., 2008; Sander et al., 2001). Results of
327 one study in cats indicated no differences in Western blot patterns of cats evaluated over the
328 course of infection (Kordick et al., 1999). Results of another study indicated that antibodies in
329 sera of infected cats reacted with an increasing number of bands of polyacrylamide gel-separated
330 proteins over the course of infection (Freeland et al., 1999). In a recent report of naturally
331 infected cats, the PPV of a Western blot test for presence of *Bartonella* DNA in cat blood was
332 reported to be only 18.8% (Lappin et al., 2008).

333 Nucleic Acid Detection: Standard PCR testing for the presence of *Bartonella* DNA may be no
334 more sensitive than blood culture for detection of active *Bartonella* infection, and detecting DNA
335 does not always equate to detection of living organisms. Nested PCR testing may increase
336 sensitivity for detection of *Bartonella* DNA in cat blood, although the risks of contamination
337 with this procedure are recognized, and laboratory precautions to minimize this risk are essential
338 (Roy et al., 2001). Real-time PCR testing also improves sensitivity with less likelihood of
339 contamination. Additional benefits of PCR testing are that the species and/or strain of
340 *Bartonella* may be identified by sequencing of the reaction product, and results of PCR testing
341 are available more quickly than those of blood culture (Fenollar and Raoult, 2004). Blood
342 samples for PCR testing should be obtained using sterile technique. Care must be taken in

343 collection and sample processing to avoid sample contamination and DNA degradation.
344 Laboratories experienced in molecular diagnostics should be used, and should be contacted for
345 submission guidelines. Numerous primer pairs are utilized for PCR testing; these vary by
346 laboratory, and primer pairs utilized by commercial laboratories may be proprietary. Broad
347 range primers are useful for detecting the presence of any *Bartonella* DNA in clinical samples,
348 and more species-specific sets of primers may be utilized to determine *Bartonella* species.
349 Multiple approaches, including multilocus sequence typing (MLST) and multiple locus variable
350 number tandem repeat analysis (MLVA) have been utilized for *B. henselae* species typing
351 (Iredell et al., 2003; Monteil et al., 2007; Bouchouicha et al, 2009a).

352 **Dogs:** Many clinical conditions that have been proposed to be attributable to canine
353 bartonellosis may also result from other etiologies. *Bartonella* infection should always be
354 considered when working with dogs with endocarditis, and for some instances of granulomatous
355 disease, however, for other clinical entities, determining for which dogs clinical signs are likely
356 to be caused by *Bartonella* infection may be difficult. Clinical conditions may be a result of co-
357 infection with multiple pathogens, particularly multiple arthropod-transmitted pathogens.

358 Bacterial isolation: Culture appears to be insensitive for diagnosis of canine bartonellosis.
359 Blood cultures of experimentally infected dogs remained positive only through 42 days PI in
360 most dogs, whereas DNA was detected in peripheral lymph nodes by PCR at up to 142 days PI
361 and in the liver at 247 days PI (Pappalardo et al., 2000a; Pappalardo et al., 2001). It is possible
362 that DNA detected by PCR was that of organisms that were not viable, but this is considered
363 unlikely. The use of an insect growth medium enriched with multiple micronutrients and
364 defibrinated sheep blood for pre-enrichment culture of blood and potentially other tissues,
365 followed by PCR testing of the liquid culture and sub-inoculation of the liquid culture onto agar

366 plates, may enhance the sensitivity of culture for diagnosis of *Bartonella* infections of dogs
367 (Duncan et al., 2007b; Maggi et al., 2005a).

368 Serologic testing: Serologic testing is available for several *Bartonella* species. Dogs may not
369 remain serologically positive for long periods. Experimentally infected dogs produced serum
370 IgG antibodies to *B. vinsonii* subsp. *berkhoffii* that peaked at reciprocal titers as high as 4096
371 within the first 1-4 weeks post-inoculation (PI). Antibody titers then declined but remained
372 increased above a reciprocal titer of 64 in some dogs through at least 243 days PI in one study
373 and 132 PI days in another study (Pappalardo et al., 2000a; Pappalardo et al., 2001).

374 There is growing evidence that dogs naturally infected with *Bartonella* (as determined by PCR
375 testing) may be seronegative (Diniz et al., 2007; Duncan et al., 2008). How widespread this
376 phenomenon is has yet to be determined, but it suggests that serology is not as sensitive a test for
377 dogs as it is for cats.

378 Nucleic Acid Detection: As noted for cats, PCR testing may be more sensitive than serology or
379 bacterial culture for detecting *Bartonella* DNA in dog tissues. Guidelines for molecular
380 diagnostic testing as noted for cats apply. A combination of use of an enriched culture medium
381 with PCR testing may be the most sensitive means of detecting *Bartonella* infection in dogs
382 (Duncan et al., 2007b).

383 THERAPY

384 Documenting clearance of *Bartonella* infections through antibiotic treatment is difficult
385 due to the prolonged relapsing bacteremia of most infected cats, and the potential difficulty in
386 detecting *Bartonella* in dogs. No regimen of antibiotic treatment has been proven effective, in
387 controlled studies with long-term follow-up, for definitively eliminating *Bartonella* infections in
388 cats or dogs (Bergmans et al., 1996; Greene et al., 1996; Kordick et al., 1997; Regnery et al.,

389 1996). Enrofloxacin (5.4–7.6 mg/kg, given PO every 12 hours) for 14 or 28 days appeared to
390 clear *B. henselae* or *B. clarridgeiae* infection in 4 of 6 or 5 of 7 treated cats, respectively, that
391 were followed for 12 weeks after treatment (Kordick et al., 1997). However, enrofloxacin causes
392 retinal degeneration in cats, and use of doses of greater than 5 mg/kg per day is contraindicated
393 (Wiebe, 2002). Doxycycline (4-12 mg/kg, given PO, every 12 hours) cleared bacteremia in only
394 1 of 6 cats treated for 14 days and 1 of 2 cats treated for 28 days (Kordick et al., 1997).
395 Antibiotics tested in another study, including erythromycin (11 to 22 mg/kg every 8 hours),
396 amoxicillin (11 to 22 mg/kg every 8 hours), and tetracycline hydrochloride (13.75 mg/kg every 6
397 hours), rapidly decreased the level of bacteremia in infected cats. Treated and untreated cats
398 became blood-culture negative after the same period of time, however, making proof of efficacy
399 of antibiotics difficult (Regnery et al., 1996). In some studies, cats were not followed for more
400 than 8 weeks after treatment, thereby making it difficult to assess drug efficacy due to the
401 possibility of chronic relapsing bacteremia in those cats (Greene et al., 1996; Regnery et al.,
402 1996). Azithromycin (various doses), a macrolide antibiotic with good intracellular penetration, has
403 been recommended for treatment of infected dogs and cats, but data from controlled efficacy studies
404 with long-term follow-up are lacking. Azithromycin appears to have important immunomodulatory
405 and anti-inflammatory properties in addition to a broad antimicrobial spectrum of activity (Culic et
406 al., 2002; Labro, 2000; Labro and Abdelghaffar, 2001; Ortega et al., 2004). These properties may
407 make it difficult to determine whether beneficial effects reported following azithromycin treatment
408 of cats are a result of anti-*Bartonella* activity, or instead are a result of the antimicrobial action of
409 azithromycin on other bacteria, of azithromycin's other properties, or of some combination of all of
410 these.

411 Routine treatment with antibiotics may induce resistant strains of any bacterial species,
412 therefore treatment should be reserved for use only in *Bartonella*-positive animals showing clinical
413 signs. Client education regarding the uncertainty of treatment efficacy, the importance of prolonged
414 follow-up, and the possibility of re-infection following treatment, is necessary. The importance of
415 flea control and other means of preventing transmission (see Prevention) should be emphasized.
416 The American Association of Feline Practitioners Panel Report on feline *Bartonella* infections is a
417 good resource for questions regarding feline bartonellosis diagnosis, treatment and prevention
418 (Brunt et al., 2006).

419 Dogs showing clinical signs of disease may benefit from treatment for *Bartonella* infection.
420 The optimal antibiotic treatment regimen is not well-documented. Treatment with doxycycline,
421 azithromycin, enrofloxacin and other antibiotics has been reported (Breitschwerdt and Chomel,
422 2005). There are no published randomized controlled clinical trials of antibiotic treatment for
423 bartonellosis in dogs.

424 PREVENTION

425 Prevention of *Bartonella* infections is best accomplished by avoiding exposure to
426 infected animals and arthropod vectors. Vector control measures are effective for interrupting
427 transmission of *B. henselae* among cats (Bradbury and Lappin, 2009). *Bartonella henselae* and
428 *B. clarridgeiae* have been transmitted through inoculation of infected cat blood, therefore cats
429 should not receive blood transfusions from cats of unknown *Bartonella* status or from cats that
430 are culture or seropositive for *Bartonella* (Kordick and Breitschwerdt, 1997; Wardrop et al.,
431 2005). It is not known how long *Bartonella* may survive in stored blood; there is one report of
432 survival of *B. henselae* in stored human red blood cells for up to 35 days (Magalhães et al.,

433 2008). Similar precautions may apply to dogs. A vaccine to prevent *Bartonella* infection in cats
434 or dogs is not available.

435 BARTONELLOSIS IN OTHER ANIMAL SPECIES

436 *Bartonella* infections are reported in horses and some domestic and wild ruminants. *Bartonella*
437 infection is common in many species of small, wild rodents, and has also been reported in marine
438 mammals, bats, and other species. There are reports indicating transmission of *Bartonella*
439 infection from rodents to human beings (Iralu et al., 2006; Kosoy et al., 2003; Welch et al.,
440 1999).

441 *Bartonella bovis* bacteremia appears to be common in dairy and beef cattle, with
442 prevalences of greater than 50 percent in some dairy herds and beef herds (Breitschwerdt et al.,
443 2001; Cherry et al., 2009; Maillard et al., 2006; Martini et al., 2008). As discussed for cats, it
444 may be difficult to attribute clinical conditions in cattle to *Bartonella* infection due to the high
445 prevalence of *Bartonella* bacteremia in this species. Endocarditis attributable to *B. bovis* was
446 reported in two French cows (Maillard et al., 2007). Results of another study indicated that
447 cattle, a reservoir host for *B. bovis*, rarely show clinical signs of infection. Interestingly, cattle
448 with *B. bovis* bacteremia had a statistically significantly shorter interval from calving to
449 breeding, and fewer retained placentas, than did cattle that were not bacteremic (Maillard et al.,
450 2006). Other *Bartonella* species detected in healthy cattle include *B. chomelii* and *B. henselae*
451 (Cherry et al., 2009; Maillard et al., 2004a). *Bartonellas* have been detected in biting flies, and
452 these arthropods may be vectors for transmission of *Bartonella* species among cattle (Chung et
453 al., 2004; Halos et al., 2004).

454 A recently described *Bartonella*, *candidatus* *B. melophagi*, was isolated from commercial
455 sheep blood and has been isolated from sheep keds also. It is likely that domestic sheep are

456 reservoir hosts for this *Bartonella* species, and that a primary vector is the sheep ked. To date,
457 there are no reports of clinical disease in sheep associated with *Bartonella* species, and no
458 information regarding prevalence of *Bartonella* infections in sheep (Bemis and Kania, 2007).
459 *Candidatus B. melophagi* was recently isolated from the blood of two ill human beings,
460 however, the clinical importance of this organism in the illnesses of those individuals has not
461 been established (Maggi et al., 2009). *Bartonella* are also reported from wild elk and deer
462 (Bermond et al., 2002; Chang et al., 2000b; Dehio et al., 2001; Maillard et al., 2004b).

463 *Bartonella henselae* has been reported in 3 horses, one with vasculitis, one with chronic
464 arthropathy, and one aborted fetus (Johnson et al., 2009; Jones et al., 2008). Whether *B.*
465 *henselae* or other *Bartonella* species have a role as pathogens in horses or sheep remains to be
466 determined.

467 It was recently suggested that *Bartonella* may be a cause of endocarditis in sea otters
468 (Chomel et al., 2009c). *Bartonella* species have also been detected in whales and porpoises
469 (Harms et al., 2008; Maggi et al., 2005b).

470 PUBLIC HEALTH

471 Several *Bartonella* species or subspecies are considered zoonotic or possibly zoonotic,
472 including but not limited to, *B. henselae*, *B. clarridgeiae*, *B. koehlerae*, *B. vinsonii* subsp
473 *berkhoffii*, *B. vinsonii* subsp. *arupensis*, *B. grahamii*, *B. elizabethae*, *B. tamiae*, *B. alsatica*,
474 *candidatus B. washoensis*, and *candidatus B. rochalimae* (Breitschwerdt and Chomel, 2005;
475 Chomel et al., 2009c; Lin et al., 2008).

476 *Bartonella* spp. cause a wide variety of clinical syndromes in people, for example, CSD
477 (typical and atypical forms, including encephalopathies in children); bacillary angiomatosis and
478 peliosis; relapsing fever with bacteremia; endocarditis; optic neuritis; pulmonary, hepatic, and

479 splenic granulomas; osteomyelitis and many others (Florin et al., 2008; Massei et al., 2005;
480 Massei et al., 2000). Immunocompetent individuals may have more localized infections,
481 whereas infections in immunocompromised individuals may more often be systemic and can be
482 fatal. As previously noted, there is more information available about zoonotic *B. henselae*
483 infections than for other zoonotic *Bartonella* infections. In one study, a high prevalence of
484 antibodies to *B. henselae* was found among Italian children without evidence of obvious illness
485 (Massei et al., 2003). This suggests that exposure and asymptomatic infection may have
486 occurred early in life with spontaneous resolution, although the possibility of long-term
487 asymptomatic infection must be considered.

488 *Bartonella henselae* isolates from people and their animal contacts have been shown to
489 be related, thus indicating the animals as sources of human infection (Bouchouicha et al., 2009b;
490 Breitschwerdt et al., 2007; Chang et al., 2002a). Different *B. henselae* types may induce varying
491 pathologic features in infected people, and certain types have been proposed to be more likely
492 associated with human disease than others (Arvand et al., 2007; Bouchouicha et al., 2009b;
493 Woestyn et al., 2004). Some studies do not support these conclusions, however, and further
494 work is required to discern what *Bartonella henselae* types are associated, for example, with
495 human disease or feline colonization (Lindroos et al., 2006).

496 Cats are the primary reservoir and vector for transmission of *B. henselae* and probably
497 also *B. clarridgeiae* to human beings. The role of arthropods in direct transmission of *Bartonella*
498 to human beings is not certain. Transmission of *B. henselae* from cats to human beings is
499 believed to occur most commonly through contamination of scratches with flea excrement
500 (Chomel et al, 1996). Transmission may also occur through cat bites if cat blood or flea
501 excrement contaminate the bite site (Chomel et al., 1996; Finkelstein et al., 2002). It has been

502 suggested that *B. henselae* and *B. vinsonii* subsp. *berkhoffii* may be transmitted by dog bites or
503 scratches, and *Bartonella* species have been detected by PCR in oral swabs collected from dogs
504 (Duncan et al., 2007a; Keret et al., 1998; Rolain et al., 2009). *Bartonella vinsonii* subspecies
505 *arupensis*, *B. elizabethae*, *B. grahamii*, and *B. washoensis* are believed to be transmitted via
506 contact with rodents (Iralu et al., 2006; Kosoy et al., 2003). The role of animals in the
507 epidemiology of *B. quintana* infections is not clear.

508 Pet owners should be informed of the current understanding regarding how cats and dogs
509 acquire *Bartonella* infections, and how these infections may be transmitted to people, including
510 the association of flea infestation or ticks with transmission. Given the number of other animal
511 species in which *B. henselae* has been detected, other means of transmission (including other
512 arthropod vectors) should be considered, and caution exercised when handling animals of any
513 species.

514 Common sense precautions for avoiding transmission of *Bartonella* spp. from animals to
515 human beings include excellent flea and tick control, avoiding interactions that result in scratches
516 or bites, thoroughly washing bite or scratch wounds, seeking medical attention when necessary,
517 and acquiring new pets of known good health status that are and have been ectoparasite free.
518 Stray or impounded cats less than 1 year old are most likely to be bacteremic with *B. henselae*
519 (Chomel et al., 1995). The United States Centers for Disease Control, the National Institutes of
520 Health, and the Infectious Diseases Society of America Guidelines for Prevention and Treatment
521 of Opportunistic Infections in HIV-Infected Adults and Adolescents, and HIV-exposed and HIV-
522 Infected Children recommend the following when acquiring a new cat: adopt a cat older than 1
523 year of age that is in good health and flea-free, avoid rough play with cats, maintain flea control,
524 wash any cat-associated wounds promptly, and do not allow a cat to lick wounds or cuts. The

525 Guidelines note that there is no evidence to indicate any benefit to cats or their owners from
526 routine culture or serologic testing of cats for *Bartonella* infection (Kaplan et al., 2009;
527 Mofenson et al., 2009). There are not specific recommendations in that document regarding
528 *Bartonella* and other companion animal species.

529 SUMMARY

530 A great deal has been learned about *Bartonella* infections recently, and much more discovery lies
531 ahead. A large proportion of domestic and non-domestic animals harbor persistent *Bartonella*
532 spp. infections. Ongoing and future studies will help to ascertain what the possible ramifications
533 of chronic *Bartonella* bacteremia may be for animal health. Veterinarians should be aware of the
534 high prevalence of feline *Bartonella* bacteremia, and carefully consider their approach to
535 evaluating cats for possible *Bartonella*-related clinical conditions. Based on current knowledge,
536 healthy cats and dogs should not be routinely tested for *Bartonella*, and antibiotic treatment for
537 *Bartonella* should not be routinely recommended for healthy cats and dogs. When ill animals are
538 treated, treatment should always be accompanied by comprehensive vector control measures, and
539 client education. Client education should emphasize the role of arthropod vectors in *Bartonella*
540 transmission, other potential avenues for transmission, and also address the potential risks
541 associated with antibiotic treatment, the likelihood of re-infection of an animal with *Bartonella*
542 following antibiotic treatment, and the zoonotic potential of *Bartonella*.

543 **Conflict of Interest:** None

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545

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