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American Association of Feline Practitioners 2006 Panel report on diagnosis, treatment, and prevention of *Bartonella* spp. infections

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A syndrome of fever, malaise, and regional lymphadenopathy in people that was frequently associated with contact with kittens or cats was called Cat Scratch Disease (CSD) for decades (Debre et al 1950). A novel organism, *Rochalimaea henselae*, was recognized (Regnery et al 1992a,b) and then was associated with CSD shortly thereafter (Zangwill et al 1993). A proposal to unify the genera *Rochalimaea* and *Bartonella* was made in 1993 and the organism was renamed *Bartonella henselae* (Brenner et al 1993). Since that time, over 2500 manuscripts regarding *B henselae* or related organisms have been published and there have been many notable discoveries concerning the diagnosis, treatment, and prevention of *Bartonella* spp. infections in both cats and people.

At the 2004 Fall Forum of The American Association of Feline Practitioners (AAFP) in San Francisco, two lectures and a roundtable discussion were presented on zoonotic diseases of cats in general (Brown et al 2002) and *Bartonella* spp. associated diseases in specific. It was noted at that time that an obvious consensus had not been reached for many issues concerning *Bartonella* spp. infections of cats. Subsequently, in the summer of 2005, the AAFP Guidelines Committee decided to convene a panel of interested individuals to develop a Panel Report on the topic. The panelists completed the first draft of this Panel Report in November 2005. The project was announced and a brief outline was presented on November 14, 2005 at the AAFP Meeting in Chicago. After approval of the

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document by the panelists, the Panel Report was distributed to select external reviewers that were considered experts in the field (see Acknowledgements). In addition, AAFP Fellows were contacted and given the opportunity to provide comments. After the comments of the external reviewers and AAFP Fellows were incorporated, the Panel Report was approved by the Guidelines Committee members and the AAFP Board in April 2006. The panel members felt that presentation of the materials would be best in a question and answer format; we used the questions that were commonly presented to us as veterinary clinicians or *Bartonella* spp. researchers. We have attempted to formulate consensus viewpoints when possible, using evidence-based medicine and thus have provided pertinent references for most statements. This Panel Report will be amended as indicated as new published data become available.

1. How are *Bartonella* spp. currently classified?

Bartonella spp. are gram-negative, hemotropic, bacterial organisms that infect people and a number of domestic and wild mammals (Brenner et al 1993, Breitschwerdt and Kordick 2000, Chomel et al 2004, Boulouis et al 2005, Guptill 2005).

2. Which *Bartonella* spp. infect cats?

By use of culture or DNA amplification techniques, cats are known to be infected by *Bartonella henselae* (Regnery et al 1992b, Koehler et al 1994, Breitschwerdt and Kordick 2000, Chomel et al 2004, Boulouis et al 2005, Guptill 2005), *B clarridgeiae* (Clarridge et al 1995, Kordick et al 1997b, Gurfield 1997, Heller et al 1997, Maruyama et al 2000), *B koehlerae* (Avidor et al 2004, Droz et al 1999, Rolain et al 2003a), *B quintana* (La et al 2005) and *B bovis* (Regnery et al 2000, Bermond et al 2002). Cats are thought to be the main reservoir hosts for *B henselae* and *B clarridgeiae* and probably are the reservoir for *B koehlerae* (Boulouis et al 2005). There is limited information about other *Bartonella* spp. infections of cats and the role of cats in the ecology of other *Bartonella* spp. is unknown. In serological studies, antibodies against *B quintana* (Al-Majali 2004) and *B elizabethae* (Hjelm et al 2002) have been detected in some cats. Because of serological cross reactivity among *Bartonella* spp., results of prevalence estimates based on serology should be interpreted cautiously.

3. Which of the *Bartonella* spp. known to infect cats are associated with CSD or other human syndromes?

The large majority of people with CSD, bacillary peliosis, or bacillary angiomatosis have been infected by *B henselae* or *B quintana* (Koehler et al 1992, 1997, Breitschwerdt and Kordick 2000, Chomel et al 2003a, 2004, Boulouis et al 2005). Persistent fever has also been detected in people infected by *B henselae* (Jacobs and Schutze 1998). Based on serological test results, *B clarridgeiae* has been suspected as a cause of CSD-like illness in people (Clarridge et al 1995, Kordick et al 1997b). *Bartonella koehlerae* DNA was recently amplified from the blood of a person with endocarditis (Avidor et al 2004). *Bartonella quintana* infection is the cause of trench fever, endocarditis, bacillary angiomatosis and other clinical conditions (Slater and Welch 2004). However, *B quintana* is transmitted to people by lice; cats are not thought to be an important factor in transmission to people.

4. Are there multiple variants of *B henselae*?

There is marked genetic diversity among *B henselae* isolates from cats. Two 16S rRNA genotypes, genotype I (Houston) and genotype II (Marseille) of *B henselae* exist and other methods of genetic classification define additional differences. Prevalence of Type I and Type II genotypes in cats or people has been most widely reported on and results varied in different studies which may relate to geographical or other factors (Gurfield et al 1997, Heller et al 1997, Koehler et al 1997, Sander et al 1998, Maruyama 2000, Guptill et al 2004, Fabbi et al 2004). Results of multilocus sequence typing (MLST) suggest that the type II genotype is ancestral with the type I appearing later and that horizontal gene transfer occurs with *Bartonella* (Iredell et al 2003). Most studies suggest that strains that infect humans are less genetically diverse than those that infect cats (Arvand et al 2001, Dillon et al 2002, Iredell et al 2003). Genetic variations between isolates may also relate to virulence in people (Bergmans et al 1996, Chang et al 2002, Dillon et al 2002, Iredell et al 2003, Woestyn et al 2004).

5. How common are *Bartonella* spp. infections of cats around the world?

Bartonella spp. infections of cats have been documented by culture or amplification of DNA by PCR assay in multiple countries within Europe, Asia, Oceania, and the Americas; an extensive review is available (Boulouis et al 2005). Prevalence rates vary dramatically, but bacteremia is commonly detected in greater than 20% of cats tested. For example, in cats between 3 months and 2 years of age residing in Florida, 33% were culture positive for a *Bartonella* spp. in blood at the time of sampling (Guptill et al 2004). Overall, *B henselae* and *B clarridgeiae* are the most common *Bartonella* infections detected in studies of cats throughout the world, and prevalence rates vary among countries (Chomel et al 2004, Boulouis et al 2005). Depending on the population tested, serological evidence of exposure can be extremely common; 93% of feral cats in North Carolina, USA had antibodies against *Bartonella* spp. (Nutter et al 2004). In general, the seroprevalence rate by study is generally about twice the rate of bacteremia in the same population. For example, in one study of 271 cats, 65 (24%) cats had *B henselae* bacteremia and 138 (51%) cats were seropositive for *B henselae* antibodies (Guptill et al 2004). In the United States, increased risk for seropositivity parallels increasing warmth and precipitation (Jameson et al 1995), which are also factors important for increased exposure to potential arthropod vectors.

6. Where does *Bartonella henselae* reside in infected cats?

Bartonella henselae mainly infects erythrocytes and endothelial cells but can also be found in a variety of tissues and in some cases has been documented extracellularly (Kordick and Breitschwerdt 1995, Kordick et al 1999, Mehock et al 1998, Guptill et al 2000, Rolain et al 2001).

7. What cats are most likely to acquire bartonellosis?

In most surveys, likelihood of *B henselae* or *B clarridgeiae* bacteremia of cats is greatest in young cats and cats infested with fleas (Chomel et al 1995, Foley et al 1998, Gurfield et al 2001, Guptill et al 2004, Boulouis et al 2005). Other risk factors include being allowed outdoors or being otherwise associated with multiple cats.

8. How are *Bartonella* spp. transmitted between cats?

In experimental studies, cats have successfully been infected with *Bartonella* spp. by intradermal, subcutaneous, intramuscular, intravenous, and oral inoculation of plate grown bacteria or blood derived from infected cats (Greene et al 1996, Regnery et al 1996, Abbott et al 1997, Guptill et al 1997, 1998, 1999, Kordick et al 1997a,b, 1999), exposure to *Ctenocephalides felis* (Chomel et al 1996), and by intradermal injection of infected flea feces (Foil et al 1998). *Bartonella henselae* is ingested by fleas while they are ingesting cat blood, the infection is amplified in the flea hindgut, and live *B henselae* is present in flea feces for at least 9 days (Higgins et al 1996, Foil et al 1998, Finkelstein et al 2002). Based on these results and those of epidemiological studies linking *Bartonella* spp. infection or exposure to cats allowed outdoors or exposed to fleas, it is the consensus opinion that exposure to fleas or flea feces is the most important consideration for transmission of *Bartonella* spp. between cats. However, *Bartonella* spp. DNA has also been detected in ticks and biting flies and so the role of other blood-feeding parasites in the transmission of bartonellosis should be further explored (Chang et al 2001, Chung et al 2004). In contrast to these successful or possible means of spread, *B henselae* was not transmitted from infected queens to kittens during gestation, by milk, or from infected queens to toms during breeding (Abbott et al 1997, Guptill et al 1998).

9. How common are *Bartonella* spp. infections in cat fleas?

Bartonella spp. have been identified in *C felis* culture or result of PCR assay in many countries, including France (La Scola et al 2002, Rolain et al 2003b), Thailand (Parola et al 2003), USA (Koehler et al 1994, Chomel et al 1996, Lappin et al 2006), New Zealand (Kelly et al 2005), Japan (Ishida et al 2001), and the United Kingdom (Shaw et al 2004). In one study of fleas collected from 92 client-owned cats residing in Alabama, Maryland, or Texas in the USA, the prevalence rates for *B henselae* and *B clarridgeiae* DNA were 22.8% and 19.6%, respectively (Lappin et al 2006).

10. Do blood-feeding arthropods transmit *Bartonella* spp. infection to people?

Many people with *B henselae*-associated illnesses have a history of close contact with kittens (Zangwill et al 1993, Tappero et al 1993, Breitschwerdt and Kordick 2000, Chomel et al 2004, Slater and Welch 2004, Boulouis et al 2005, Guptill 2005). Most people with *Bartonella* infections are believed to have been scratched and therefore likely to have had *Bartonella* spp. inoculated into their skin by a cat. Infected flea feces or infected cat blood are likely to contaminate cat claws during grooming, ultimately contaminating cat scratches with *Bartonella* spp. (Foil et al 1998). It is also possible that *Bartonella*-infected flea feces could enter the body through any broken skin. In Parinaud's oculoglandular syndrome, it is possible that flea feces containing the organism contaminate the conjunctiva, starting the syndrome (Cunningham and Koehler 2000). Some people with *Bartonella* spp. antibodies or *Bartonella*-associated illness have not been in contact with cats. In these individuals, transmission by contact with flea feces in the environment, flea (or other arthropod) bite, or contact with other reservoirs may be have been the source of infection.

11. Are *Bartonella* spp. new infections of cats?

Recently DNA of *B henselae* was amplified from the dental pulp of cats that lived over 800 years ago (La et al 2004). Thus, the organisms are not new to cats, but are newly recognized. Factors associated with the emergence of zoonotic *Bartonellae* were recently reviewed (Boulouis et al 2005). Factors cited included recent use of advanced diagnostic tools allowing for increased sensitivity of detection, increasing populations of immune deficient individuals predisposed to disease, presence of co-infections that might amplify disease, increases in outdoor activity, or rural housing that may increase risk for exposure, and spread of the organisms around the world by transport of infected reservoir hosts (Boulouis et al 2005).

12. What are the clinical manifestations of *Bartonella henselae* infections of people?

In people, *B henselae* infection is most commonly associated with CSD, peliosis hepatis, bacillary angiomatosis, endocarditis, bacteremia, neuroretinitis, and encephalopathy (Carithers 1985, Margileth 1987, Koehler et al 1992, Rolain et al 2004). Immunocompetent people are more likely than immunodeficient people to develop classical CSD. After cat scratch transmission, a papule followed by a pustule develops at the site of inoculation within 14 days. Regional lymphadenopathy usually develops within weeks after inoculation; abscessed nodes are common (Carithers 1985, Margileth 1987). Most cases of uncomplicated CSD are self-limiting, may take several months to completely resolve, and have minimal to no response to antimicrobial treatment (Rolain et al 2004). However, complicated cases like those with central nervous system disease, visceral involvement, or retinitis are frequently prescribed antimicrobial agents; the combination of doxycycline with rifampin is common (Rolain et al 2004). Bacillary angiomatosis and peliosis hepatis are most common in immunocompromised people. In contrast to CSD, these syndromes nearly always respond to antimicrobial therapy (Rolain et al 2004) and occasionally may be fatal without antibiotic treatment.

13. How common is CSD?

In the United States, the incidence of CSD was estimated at 9.3 cases per 100,000 people per year (Jackson et al 1993). In 2000, it was estimated that hospitalization rates for treatment of CSD were 0.60/100,000 children under 18 years of age and 0.86/100,000 children under 5 years of age (Reynolds et al 2005). In that study, it was also noted by the authors that while cat ownership has increased dramatically, the prevalence rates of CSD detected in 2000 were similar to those detected in the 1980s (Reynolds et al 2005). In the Netherlands, the incidence of CSD was estimated at 12.5 cases per 100,000 people per year (Bergmans et al 1997).

14. Does exposure of people to *Bartonella* spp. always result in illness?

Bartonella spp. infection does not always result in recognized illness; clinically healthy, seropositive people have been detected in a number of studies (Noah et al 1997, Sander et al 2001, Massei et al 2004, McGill et al 2005).

15. How do *Bartonella* spp. cause disease in people?

There are many possible mechanisms for *Bartonella*-associated illness. As discussed in Question 4, pathogenic potential may vary among different *Bartonella* spp., genotypes within a species, individual isolates, and host species that is infected. In people, disease associated with *Bartonella* spp. varies according to the immune status of the host. For those who become ill, pathological changes include a focal suppurative reaction seen in classical CSD of immunocompetent people, an angioproliferative response to infection seen with bacillary angiomatosis in immune suppressed people, an endovascular proliferation of the organism seen with endocarditis, or an exaggerated inflammatory response to the organism as occurs with meningoencephalitis (Chomel et al 2003b, Resto-Ruiz et al 2003, Rolain et al 2004, Dehio 2005).

16. What abnormalities have been detected in cats experimentally inoculated with *Bartonella* spp.?

Intradermal inoculation of four cats with *B koehlerae* led to bacteremia but no detectable clinical abnormalities (Yamamoto et al 2002). Results of studies in which *B henselae* or *B clarridgeiae* were inoculated into cats experimentally have given variable clinical results but the studies cannot be compared directly because of differences in isolates used and study design (Regnery et al 1996, Abbott et al 1997, Kordick and Breitschwerdt 1997, Guptill et al 1997, 1998, 1999, Kordick et al 1999, O'Reilly et al 1999, Mikolajczyk and O'Reilly 2000, Powell et al 2002, Yamamoto et al 2002, 2003). Fever, loss of appetite, transient mild anemia, red swellings at the injection site, lymphadenopathy, exaggerated or diminished response to stimuli, aggressive behavior, focal seizures, nystagmus, and generalized tremors were detected transiently in some cats.

Histopathological lesions have been detected in some cats experimentally inoculated with *B henselae* or *B clarridgeiae* (Guptill et al 1997, Kordick et al 1999). Peripheral lymph node hyperplasia, splenic follicular hyperplasia, splenic microabscesses and hepatic abscess, lymphocytic cholangitis/pericholangitis, lymphocytic hepatitis, lymphoplasmacytic myocarditis, and interstitial lymphocytic or pyogranulomatous nephritis were detected in some cats (Guptill et al 1997, Kordick et al 1999). In addition, *Bartonellae* were detected in multiple tissues from experimentally inoculated cats. The results of these studies suggest that *Bartonella* spp. infection could be considered on the differential list for a number of medical problems in cats. However, the panel believes that further work is needed to determine what actual causal associations may exist among *Bartonella* spp. infections and any clinical syndromes in cats (see discussion of Question 17).

17. Do studies of naturally infected cats suggest an association between *Bartonella* spp. infection and illness?

The consensus opinion of the panel and external reviewers is that much more work will be required to determine the spectrum of *Bartonella* spp. associated illness in cats since most naturally infected cats exhibit no clinical signs. There have been only a few peer-reviewed reports documenting *Bartonella* spp. associated illness in naturally exposed cats. One fatal case of *B henselae*-associated endocarditis was reported in a cat (Chomel et al 2003b). Several case reports provide evidence of *Bartonella* spp. exposure in cats with ocular disease and subsequent response to therapy with drugs with presumed *Bartonella* activity (Lappin and Black 1999, Ketring et al 2004). Peer-reviewed seroepidemiologic studies have been published from the United States (Breitschwerdt et al 2005), Japan (Ueno et al 1996) and Switzerland (Glaus et al 1997). In the study from Switzerland, prevalence rates were similar in ill and clinically healthy cats but the ill *B henselae* seropositive cats were more likely than the ill seronegative cats to have stomatitis and diseases of the urinary system. In the study from Japan, coinfection of cats with feline immunodeficiency virus and *Bartonella* spp. was associated with an increased risk of lymphadenopathy and gingivitis. In the study from the United States, ill *B henselae* seropositive cats were more likely than ill seronegative cats to have hematuria. Local production of *Bartonella* spp. antibodies and *Bartonella* spp. DNA have been detected in aqueous humor of cats previously presumed to have idiopathic uveitis but a cause and effect was not established (Lappin et al 2000). Many of the studies are based on serological test results and such results document exposure but not necessarily active infection.

In addition, because serological test results do not confirm the *Bartonella* spp. associated with the infection (Question 2), the role each *Bartonella* spp. that infects cats plays in the induction of clinical disease is unknown. Many chronic conditions may be the result of multiple factors acting together, or else just coincidental occurrence and thus, clearly linking a syndrome with an organism like *Bartonella*, which has a long history of association with its reservoir host, will be challenging (See Question 22).

18. What *Bartonella* spp. tests are available for use with cats?

Culture of blood or tissues, amplification of *Bartonella* DNA by PCR assay of tissue and body fluids, and detection of antibodies in serum, aqueous humor, or CSF can be used to assess individual cats for *Bartonella* infection and are commercially available in the United States and some other countries.

19. How can culture results be used to aid in the diagnosis of feline bartonellosis?

Proving the presence of *Bartonella* spp. in blood or tissues indicates current infection and it is our consensus opinion that culture is the gold standard technique for proving infection. The major limitations are the requirement for a specialized laboratory and the length of time for return of results because of the slow growth of the organisms. There are many seropositive, culture result-negative cats; it has often been assumed these cats had eliminated the infection. However, other possibilities are: the bacteremia was intermittent (Kordick and Breitschwerdt 1997) and not present in the sample cultured; the number of organisms were below the sensitivity limit of the assays; the organism died in transport to the laboratory; the culture was not held long enough; or the serological test result was falsely positive. New media to support the growth of *Bartonella* spp. in culture have recently been reported and may improve the ability to culture *Bartonella* spp. from blood or other tissues of cats (Maggi et al 2005). Although positive blood culture results prove *Bartonella* spp. infection in cats, they do not prove the cat is clinically ill from the infection.

20. How can PCR assay results be used to aid in the diagnosis of feline bartonellosis?

Amplification of *Bartonella* spp. DNA from feline blood in EDTA, other fluids, or tissues has been used in many studies (Lappin et al 2000, 2006, Jensen et al 2000, Maggi and Breitschwerdt 2005). There are several gene targets that have been used. PCR assays targeting the 16S−23S rRNA intergenic spacer region can be designed to amplify different species resulting in different product sizes so that a single assay can also be used to determine the species of the infecting organism(s) that was amplified (Jensen et al 2000, Maggi and Breitschwerdt 2005). PCR assays require specialized laboratories, require stringent quality control to avoid both false-positive and false-negative results, can be expensive to perform, and are currently not standardized among laboratories. However, results can be obtained more rapidly than from culture. True positive PCR assay results document presence of microbial DNA but do not prove the organism was alive or prove that the cat was clinically ill from the infection. False-negative PCR assay results could occur because of intermittent bacteremia, previous use of antibiotics, lack of microbial DNA in the sample tested, or inhibitory or interfering substances in biologic specimens. *Bartonella* spp. DNA can also be amplified from tissue, CSF, and aqueous humor; however, any blood contamination of the fluid or tissue being tested could give a positive test result. For example, even though *B henselae* DNA was amplified from the aqueous humor of some cats with uveitis, the DNA could have been present from hemorrhage associated with aqueous paracentesis or from the breakdown of the blood ocular barrier from another cause of uveitis (Lappin et al 2000).

21. How well do serological test results correlate with *Bartonella* spp. infection in cats?

Antibodies against *Bartonella* spp. have been detected in serum of cats and humans primarily by use of immunofluorescent antibody assay (IFA), enzyme linked immunosorbent assay (ELISA), or Western blot immunoassay. Use of IFA slides or ELISA plates coated with different *Bartonella* spp. have been used to attempt to determine the prevalence of exposure to different infecting

species. Western blot immunoassay has the advantage of determining the immunodominant antigens recognized by the immune response (Haimerl et al 1999, Freeland et al 1999, Chenoweth et al 2004). Many assays used for cats use whole *B henselae* organisms (IFA) or antigens (ELISA and Western blot immunoassay) for antibody detection. Antibodies against *B henselae* generally cross react with *B clarridgeiae* and other *Bartonella* spp. so a positive test result cannot discriminate the infective species. Serum antibody tests can be performed quickly and are inexpensive but there is currently no standardization among laboratories in the United States. A positive antibody test result suggests exposure to a *Bartonella* spp. but it does not prove current infection and a negative test result does not exclude infection (Pretorius et al 1999). The reported positive predictive values of IFA or ELISA (anti-IgG) serologic tests for *B henselae* or *B clarridgeiae* bacteremia are 32–46%, and the reported negative predictive values are 85–97% (Chomel et al 1995, Gurfield et al 2001, Fabbi et al 2004, Guptill et al 2004). Therefore, less than half of antibody result-positive cats may be actively infected and 3–15% of antibody result-negative cats may be bacteremic.

22. Can *Bartonella* spp. antibody tests be used to prove clinical disease in cats?

Because of the difficulty in proving clinical bartonellosis in cats, sensitivity, specificity, and predictive values of *Bartonella* spp. antibody tests for *Bartonella*-associated illness in cats have not been determined. There is no antibody class response (IgM or IgG), no antibody titer magnitude, and no antigen recognition pattern by Western blot immunoassay that consistently correlates with the presence or absence of clinical disease. While increasing antibody titers can be detected in some cats, this only indicates active infection, not clinical illness resulting from infection. Results of a *Bartonella* spp. antibody test that detects antibodies against *B henselae* and *B clarridgeiae* were compared between groups of cats with and without clinical syndromes potentially associated with *Bartonella* spp. infection (uveitis, neurological disease, and stomatitis) while controlling for age and geographical location (Pearce et al 2005, Fontenelle et al 2005, Dowers and Lappin 2005). Clinically healthy and ill cats could not be differentiated on the basis of antibody test results. Even detection of antibody production in aqueous humor does not prove clinical bartonellosis. In one study, local production of *Bartonella* spp. antibodies by the ocular tissues of cats with uveitis was documented in some cats but local antibody production also occurred transiently in healthy cats after experimental inoculation (Lappin et al 2000).

23. How can I make a clinical diagnosis of feline bartonellosis?

It is the consensus of our panel that there is no single test result that can prove clinical bartonellosis in cats. The combination of all of the following findings may aid in the diagnosis:

- presence of a syndrome reported to be associated with *Bartonella* spp. infection;
- exclusion of other causes of the clinical syndrome;
- detection of a positive *Bartonella* spp. test (culture, PCR assay, or serology); and
- response to administration of a drug with presumed anti-*Bartonella* activity.

However, as discussed in Question 22, results of serological tests alone do not prove current infection. In addition, because the antibiotics used for the treatment of bartonellosis in cats generally have a broad spectrum and are effective for other infecting organisms which can cause syndromes resembling bartonellosis, even when these criteria are fulfilled, the diagnosis of clinical feline bartonellosis is not definitive.

24. What antibiotics are most likely to be effective for treatment of cats with a clinical illness attributable to bartonellosis?

Because the diagnosis of feline bartonellosis is difficult and has not been standardized, optimal anti-microbial protocols for clinical feline bartonellosis are unknown. Much of the information concerning treatment of bartonellosis in cats was derived from studies of people. In vitro, *Bartonella* spp. are susceptible to many antibiotics (Maurin et al 1995, Kordick et al 1997b, Rolain et al 2004) but antibiotic susceptibilities do not correlate with clinical efficacy

in people. Even in people for whom well-defined clinical syndromes are recognized, a consensus on optimal use of antibiotic therapy is not always reached (Rolain et al 2004). Antibiotic failure or success may relate to the pathogenesis of the individual syndrome and the immune status of the host. For example, in immunocompetent people with classical CSD, the organism is often present in low numbers in lymph nodes by the time of biopsy. In this situation, the clinical manifestations of disease may relate to the immune-mediated clearance of the organism, not organism replication explaining antimicrobial failure. Failure of antibiotic treatment may be related to the intracellular location of the *Bartonella* organism and replication rates (Schulein et al 2001, Seubert et al 2002). In studies of *B tribocorum* infection of rat erythrocytes, it was shown that after a brief period of intraerythrocytic replication, the organism persisted in a non-replicating state (Schulein et al 2001). While many of the drugs used to treat CSD in people penetrate cells very well, each is primarily dependent on bacterial replication. In individual case reports in cats, therapeutic responses have been reported with doxycycline or azithromycin (Lappin and Black 1999, Ketring et al 2004). Both of these antibiotics have extensive antibacterial spectrums and also modulate immune responses, therefore apparent therapeutic responses may be related to anti-inflammatory effects (Culic et al 2002, Lee et al 2004). However, the extent of these anti-inflammatory effects in cats is unknown. In a double-blind, placebo controlled trial of children with CSD, administration of azithromycin led to a more rapid decrease in lymph node volume, but not other clinical parameters, when compared to placebo (Bass et al 1998). The panel recommends consulting the AVMA and AAFP statements (www.avma.org/scienact/jtua/default.asp) on judicious use of antimicrobial agents prior to antibiotic selection. It is the consensus opinion of the panel that in general, drugs commonly used for humans (ie, fluoroquinolones and azithromycin), should not be prescribed for routine bacterial infections of cats if an alternate choice is available. Doxycycline administered at 10 mg/kg, PO, q12–24 h or amoxicillin–clavulanate at 22 mg/kg, PO, q12 h for 7 days may be appropriate first choices for *Bartonella*-positive cats for which a definitive diagnosis is not known. If there is a positive response, treatment should be continued. If the cats have persistent clinical signs after 7 days and a further exhaustive search for an etiology has not yielded a definitive diagnosis, switching to azithromycin (10 mg/kg, PO, daily for 1 week followed by q48 h) or a fluoroquinolone may be indicated. Optimal duration of therapy for any drug has not been determined, however, because the organisms are intracellular, continuation of treatment for a minimum of 2 weeks and at least 1 week past resolution of clinical illness may be prudent. Because cats with clinical bartonellosis are likely bacteremic, extreme care should be taken to avoid being bitten or scratched while administering drugs. Precautions should be used when administering doxycycline to help minimize esophageal irritation and stricture (Melendez et al 2000).

25. What antibiotics can be used to clear *Bartonella* spp. bacteremia in cats?

Duration of bacteremia without treatment has varied dramatically in studies of naturally infected or experimentally infected cats. In some cats, bacteremia was present for weeks and in other cats bacteremia was present for months (Kordick and Breitschwerdt 1995, Guptill et al 1997, Greene et al 1996, Kordick and Breitschwerdt 1998). Duration of bacteremia may relate to the immune status of the host as well as the *Bartonella* spp. or genotype involved with the infection. There have been several attempts to eliminate bacteremia in cats naturally infected or experimentally infected with *B henselae* or *B clarridgeiae* (Koehler et al 1994, Greene et al 1996, Regnery et al 1996, Kordick et al 1997b). Drugs evaluated have included doxycycline, amoxicillin, amoxicillin–clavulanate, enrofloxacin, erythromycin, tetracycline HCl, and rifampin. Results of the studies were variable with bacteremia apparently being eliminated in some cats but not others. In some cats, blood culture results were initially negative after treatment but then positive at a later date. Follow-up times were limited in some studies, and clearance of *Bartonella* infection cannot truly be documented. Taken together, it is the consensus opinion of the panel that the available data indicate that the most appropriate antibiotic treatment regimens for feline *Bartonella* infections are unknown, and the optimal follow-up time for repeat testing has not been established. However, we believe that if treatment is attempted, it should be prolonged and combined with eradication of fleas on all animals in the household and the premises in an attempt to avoid re-infection.

26. Is there any indication for repeating *Bartonella* spp. tests in cats?

Occasionally, repeated antibody testing might be indicated. For example, a changing antibody titer might indicate active or recently cleared infection. However, the diagnostic utility of repeated antibody testing to determine active infection or to determine clearance of bacteremia has not been documented in a peer-reviewed publication. Repeated blood culture or PCR assays can be used to document persistent infection if initial results are positive, but negative test results do not document *Bartonella* elimination (see Question 19).

27. Should clinically healthy cats be tested for *Bartonella* spp. infection?

Different authors have made varying recommendations on whether to test clinically healthy cats for *Bartonella* spp. infection. However, The Guidelines for Preventing Opportunistic Infections Among HIV-Infected Persons, jointly authored by the United States Public Health Service and the Infectious Diseases Society of America, states ''No evidence indicates any benefits to cats or their owners from routine culture or serologic testing of the pet for *Bartonella* infection'' (Kaplan et al 2002). It is the consensus opinion of this panel that there are currently not enough data concerning the benefit of performing *Bartonella* spp. tests on healthy cats to make a definitive recommendation for all cats. We believe it is prudent to discuss the advantages and disadvantages of *Bartonella* testing with each individual cat owner and document the discussion and outcome of the discussion in the medical record (Tannenbaum 1991). The following are some advantages and disadvantages concerning routine *Bartonella* spp. testing of healthy cats.

Potential advantages

- Cats with positive *Bartonella* spp. test results can be avoided, for example, for selection as blood donors or breeding animals.
- Cats with negative *Bartonella* spp. test results are less likely to be harboring the organism and so may be a safer pet than a cat with *Bartonella* spp. positive test results.
- Testing cats for *Bartonella* spp. may allow the veterinarian to avoid claims or litigation.

Potential disadvantages

- *Bartonella* spp. test results (particularly PCR and serology) can be falsely positive.
- Cats with positive *Bartonella* spp. serological test results are often considered dangerous but may have eliminated the infection and may be partially immune to re-infection.
- Detection of negative *Bartonella* spp. test results will lead to a false sense of security.
  - Cats with negative *Bartonella* spp. test results at one point in time may be falsely negative.
  - Cats with negative *Bartonella* spp. test results at one point in time can be infected and become bacteremic within 2 weeks if preventative measures are not taken.
- Detection of positive *Bartonella* spp. test results in some situations may lead to needless euthanasia.
- The expense of *Bartonella* spp. testing will lead to some owners avoiding ownership of an individual cat.
- Redistribution of limited funds to cover the expense of *Bartonella* spp. testing will result in some owners forgoing other needed and relevant health care like flea control.

28. What is the best way to prove a cat is not infected by a *Bartonella* spp.?

As discussed in the sections regarding diagnostic testing, documentation of true *Bartonella*-negative status is difficult to impossible with current testing modalities. It is the consensus of our panel that cats that are culture- or PCR-negative, and antibody-negative, are very unlikely to be a source of flea, cat, or human infection.

29. Should healthy cats be treated for *Bartonella* spp. infection?

Because of the difficulty in eliminating *Bartonella* spp. infection and because some cats that eliminate *Bartonella* spp. infection can be reinfected, there is no proven benefit to treating *Bartonella*-positive (based on any test result), healthy cats. Administration of antibiotics that fail to clear a chronic intracellular infection may result in antimicrobial resistance. Treatment may result in a false sense of security to the owner leading to less stringent avoidance of bites or scratches

and maintenance of flea control. Antibiotics can be expensive and have potential for toxicity. In addition, the increased risk to the owner from administration of the drug versus the poorly documented benefit to treatment should also be considered. In one study, the authors stated "given current concern about the development of antimicrobial resistance, we would reserve recommendation for treatment to cats owned by an immunocompromised individual or as an alternative to euthanasia of a pet" (Kordick et al 1997b). It is the consensus opinion of the panel that whether or not anti-microbial therapy is prescribed, it is imperative to also prescribe flea control measures.

30. What is the potential for development of a *Bartonella* vaccine for cats?

Naturally exposed cats have been infected with *B clarridgeiae* and *B henselae* or both genotypes of *B henselae* concurrently (Gurfield et al 2001, 2004). Results of experimental studies have demonstrated variable protection for cats from heterologous or homologous challenge (Greene et al 1996, Regnery et al 1996, Yamamoto et al 1998, 2003). Thus, available data indicate that to be effective a *Bartonella* vaccine will need to be multivalent (Yamamoto et al 1998).

31. Is bartonellosis an occupational risk factor for veterinary health care professionals?

Because veterinary health care providers commonly handle cats with previous or current flea infestation, exposure to *Bartonella* spp. infected cats is common. In one survey of 351 veterinary health care professionals in the USA, 7.1% were seropositive for *B henselae* or *B quintana* antibodies. The number of years of experience correlated to risk of seropositivity suggesting an increased risk of exposure over time (Noah et al 1997). These findings emphasize that veterinary health care professionals should avoid scratches and bites, use caution to avoid contact with flea excreta when handling flea-infested cats, immediately clean wounds thoroughly, and wash their hands immediately after every physical examination or other procedure (Brown et al 2002).

32. What is the AAFP recommendation for avoiding zoonotic bartonellosis and *Bartonella* spp. infections of cats?

The AAFP Panel recommendations that follow were adapted from Guidelines for Preventing Opportunistic Infections Among HIV-Infected Persons (Kaplan et al 2002) and the AAFP Panel Report on Zoonoses (Brown et al 2002).

- Flea control should be initiated and maintained year-round.
- If a family member is immunocompromised and a new cat is to be acquired, adopt a healthy cat >1 year of age and free from fleas.
- Discuss the advantages and disadvantages of testing healthy cats for *Bartonella* spp. infections.
- Immunocompromised individuals should avoid contact with cats of unknown health status.
- Cat claws should be trimmed regularly, but declawing of cats is generally not required.
- Scratches and bites should be avoided (including rough play with cats).
- Cat-associated wounds should be washed promptly and thoroughly with soap and water and medical advice sought.
- While *Bartonella* spp. have not been shown to be transmitted by saliva, cats should not be allowed to lick open human wounds.

The AAFP Panel recommendations for decreasing the likelihood of pet cats becoming infected with *Bartonella* spp.:

- Maintain an appropriate flea-control program year-round.
- Be cautious about adding stray cats or cats from shelters to the household without controlling fleas.
- Keep cats indoors to minimize hunting and exposure to fleas and other possible vectors.

Other issues concerning bartonellosis discussed in this document should also be considered with each individual family, for example, the complexities of diagnostic testing and the uncertainty of antimicrobial treatment efficacy. While *Bartonella* spp. are significant zoonotic agents, veterinary clinicians and their teams should focus on the entire cat and emphasize prevention of all zoonotic diseases (Brown et al 2002).

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