BARTONELLA:

FELINE DISEASES AND EMERGING ZOONOSIS

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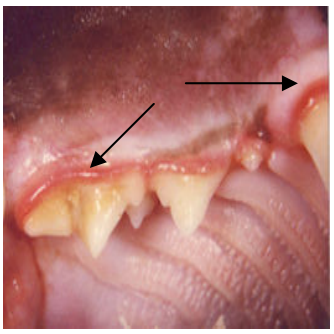

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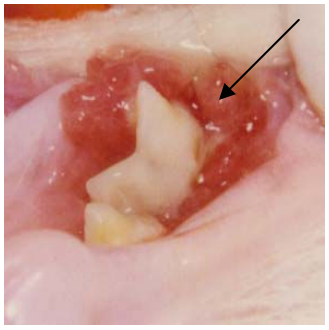

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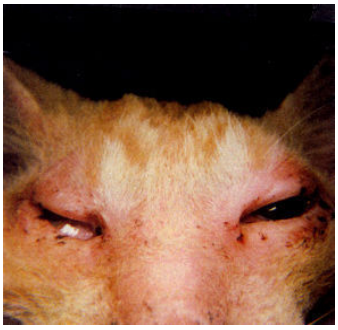

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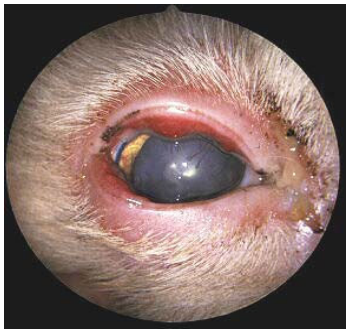

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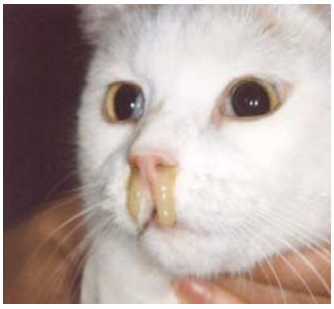

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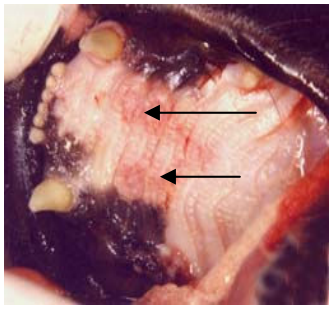

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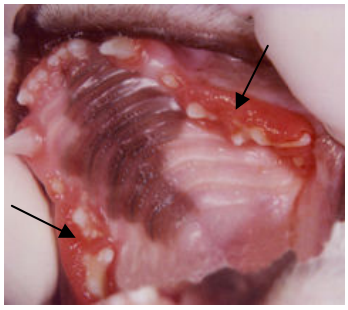

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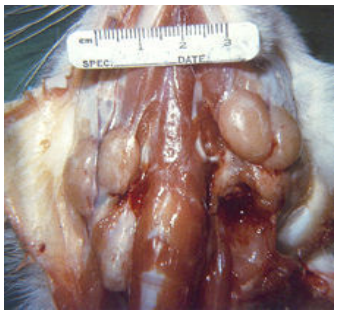

Lymphadenopathy

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Dr. Hardy is the Director and sole owner of the National Veterinary Laboratory, Inc.

SUMMARY:

Bartonella are Gram-negative, fastidious bacteria (approximately 20 species known to date) that are widespread in nature infecting many animal species from wild rodents, ruminants, pet animals, to humans. They are transmitted by arthropod vectors including fleas, ticks, biting flies, and lice from animal-to-animal (intraspecies) and species to species (interspecies). Direct animal-to-animal transmission, without vectors, probably occurs rarely and is exemplified by the transmission from cats to humans via scratches, bites, and fur contact. Most animal species have their own unique *Bartonella species* that establish chronic, possibly life-long, infections and carrier states. Only a relatively few infected animals develop a *Bartonella*-induced disease thus Koch's postulate is difficult to apply to pathogenic micoorganisms that establish long term carrier states.[29,30,44]

Cats are infected with at least 6 *Bartonella species* and most remain healthy carriers for years, or possibly, for their entire lives. However, some cats develop chronic inflammatory diseases. The mechanisms involved in the pathogenesis of *Bartonella* diseases are being elucidated rapidly. *Bartonella* possess pili which are hair-like structures found on the bacteria's surface. *Bartonella* have a strong tendency to stick or clump together in tissues and in culture and to stick to, and penetrate, erythrocytes and endothelial cells. The ability to adhere to each other, and to the membranes of erythrocytes and endothelial cells, leads to the wide and varied tissue pathogenesis observed in cats, dogs and people. Pili and a protein called deformin are probably responsible for the sticky properties.[1] The broad tissue specificity of *Bartonella* is due to the adhesion to endothelial cells which are the constituents of capillaries. *Bartonella* proteins stimulate endothelial cells to proliferate causing neovascularization or angiogenesis and an outpouring of inflammatory cytokines which recruit inflammatory cells such as lymphocytes, plasma cells and macrophages. Thus, *Bartonella* induce chronic lymphocytic plasmacytic granulomatous inflammatory reactions in vascular tissues throughout the infected animal's body. With the understanding of the pathogenic mechanisms of *Bartonella,* it is easier to understand the widespread disease distribution of *Bartonella*-inflammatory diseases in cats: oral diseases, respiratory diseases, ocular diseases, gastrointestinal diseases, skin diseases and diseases in major organs such as the spleen and liver. Infected healthy and diseased cats can be successfully treated with azithromycin, rifampin or doxycycline.

Infected cats can transmit their *Bartonella* to people via scratches (cat scratch disease), bites, or rarely, through simple contact with their fur. Some of the resulting zoonotic diseases in humans can be severe and even life threatening in children, HIV-infected healthy or AIDS patients, transplant recipients, and people on chemotherapy. It is very important for veterinarians to fully understand the biology of *Bartonella* in cats and dogs so they can become active in the public health effort to prevent the spread of these potentially dangerous microorganisms to people.

I thank the numerous practicing veterinarians for their assistance in gathering the clinical data and therapy evaluations. The clinical *Bartonella*-disease association could not have been obtained without their collaboration.

INTRODUCTION:

During the past decade there has been a major revolution in our knowledge of bacteria of the genus *Rochalimaea* which were, until recently, classified in the family *Rickettsiaceae*.[1-146] The genus *Rochalimaea* has been reclassified as the genus *Bartonella* and removed from the family *Rickettsiaceae* of the order *Rickettsiales* and placed in the family *Bartonellaceae*.[26] During this time a number of emerging *Bartonella* diseases have been described in humans, cats and dogs. There are presently more than 16 named species and numerous unnamed species included in this obscure genus: *Bartonella bacilliformis, Bartonella henselae*, *Bartonella clarridgeiae, Bartonella koehlerae*, *Bartonella weissii*, *Bartonella quintana*, *Bartonella doshiae, Bartonella taylorii, Bartonella tribocorum, Bartonella vinsonii*, *Bartonella elizabethae*, *Bartonella grahamii*, *Bartonella woshoensis, Bartonella alsatica, Bartonella schoenbuchii* and *Bartonella capreoli* . From the veterinary perspective, the most important members are *Bartonella henselae*, *clarridgeiae, koehlerae*, *weissii, elizabethae* and *vinsonii,* all of which can cause severe illnesses in cats and dogs and, all of which are zoonotic infections where cats and dogs act as natural reservoirs of the zoonotic pathogenic bacteria.[17,21-24,28,32,33,40,48,56a,60,62,64,71,73-75,83,84,100-102,111]

The most frequently occurring *Bartonella*-induced human disease is cat scratch disease (CSD) which is caused by *Bartonella henselae* and *Bartonella clarridgeiae*. CSD was first described as early as 1889.[103] *Bartonella quintana*, the louse-borne agent of trench fever, was responsible for high morbidity among Allied and Axis troops in France in World Wars I and II.[27,42] Both *Bartonella henselae* and *quintana* have been found in HIV-1 infected people and in inner city homeless people.[18,31,76-78,105,112,115,126,141] *Bartonella elizabethae* has recently been identified as a new member of the group and was isolated from a person with endocarditis and has been found to be common in cats in Sweden.[36] *Bartonella vinsonii*, which was originally isolated from a vole on an island in the St. Lawrence River and recently from pet dogs with endocarditis, has also been shown to cause a febrile culture-negative endocarditis in humans.[21-23,132]

Recent studies have shown that pet cats serve as a major persistent reservoir for five *Bartonella* species: *Bartonella henselae*, *Bartonella clarridgeiae* and *Bartonella koehlerae, Bartonella weissii*, and *Bartonella elizabethae*, with prolonged, asymptomatic bacteremia from which humans may become infected.[32,33,35,36,40,53,57,71,75,111,136,141] The cat flea, *Ctenocephalis felis* and deer and dog ticks can carry the bacterium and probably act as vectors transmitting it from cats to humans. Surprisingly, in one study 41% of the healthy cats tested were persistently bacteremic but showed no clinical signs.[75] Identification of infected cats and antibiotic treatment along with control of flea infestations are recommended for decreasing human exposure to *Bartonella* species. Untreated infected cats may remain bacteremic for life.[75] There are presently more than 60 million pet cats in nearly one-third of all US households which is a significant reservoir for human infection with this pathogenic bacterium.[140]

MICROBIOLOGY:

Bartonella species are gram-negative, aerobic, motile bacilli (rods).[26,43,46,112,128,137-139] *B. bacilliformis* is motile by a unipolar flagellum and *B. henselae* has a jerky motility without flagella. The bacteria are difficult to culture from tissues, are fastidious, but are somewhat easier to culture from blood. *In vitro* growth is enhanced when nutrient agar medium contains rabbit or sheep blood and the culture is incubated for at least 2 weeks. Isolation of organisms from blood often requires 4 to 6 weeks of incubation before colonies are apparent. Because *Bartonella* are erythrocyte-associated (internal or on their surfaces) blood culture systems that lyse erythrocytes facilitate and enhance isolation of the bacteria from blood.[79,137]

On solid agar media, colonies of *B. henselae* are white, rough, dry, and pit the agar surface.[46] Most strikingly, *B. henselae* organisms are very sticky, clumping and sticking to each other and to plastic and glass surfaces. The ability to adhere to each other, and to the membranes of RBCs and endothelial cells, leads to the wide and varied tissue pathogenesis observed in cats, dogs and people.[36,37] Specific species identification is aided by antibody serotyping, by cellular fatty-acid analysis, and by polymerase chain reaction (PCR) analysis.[14,70,72,90,91,117,120,121,123]

METHODS OF DETECTION OF *BARTONELLA* INFECTIONS:

There are several direct and indirect methods to determine *Bartonella* infections (Figure 1).[9,14,15,42,57,117,128,142] The direct isolation of the bacteria from tissues or blood is difficult due to the fastidious nature of the bacteria. Another direct method of detection is by PCR with probes specific to *Bartonella*. Indirect serological techniques are practical, economical and often superior to direct methods in that the antibody produced in response to infection is an amplification system.[57] Detection of antibody against *Bartonella* can determine current active infections or, at times, may signify past infections. Most cats with high antibody titers (>1:64) to *B. henselae* are currently infected and bacteria can often be isolated from their blood. Serologic methods include IFA, ELISA, and western immunoblot.[15,57,65]

Figure 1

METHODS FOR DETECTION OF *BARTONELLA SPECIES* INFECTION

Direct:
- Isolation: fastidious, Gold Standard??
- PCR

Indirect:
- Serology:
  - IFA
  - ELISA
  - Western Immunoblot*

Isolation from Blood:

Bartonella are difficult to culture from tissues because they are so fastidious. However, they are somewhat easier to culture from blood. Because *Bartonella* are erythrocyte-associated (internal or on their surfaces) blood culture systems that lyse erythrocytes facilitate and enhance isolation of the bacteria from blood. Isolator™ blood collection tubes (Wampole Laboratories, Cranbury, NJ) are used for *Bartonella* isolation in veterinary medicine. One ml of sterile blood is added to the lysis tube and the tube is gently inverted several times to lyse the red blood cells. The blood must be plated on blood agar plates within 6 hours. *In vitro* growth is enhanced when nutrient agar medium contains rabbit or sheep blood and the culture is incubated for several weeks. Isolation of organisms from blood often requires 4 to 6 weeks of incubation before colonies are apparent. Although this method is considered the Gold Standard, the method is insensitive and often (50%) the bacteria cannot be isolated from known infected cats. Table 1 below summarizes the comparison of culture isolation and western immunoblot results from 256 cats.

Table 1

COMPARISON OF IMMUNOBLOT TO CULTURE FOR DETECTION OF *BARTONELLA HENSELAE* INFECTION IN 256 CATS*

Immunoblot Results	Number of Cats	Culture Negative	Culture Positive	Per Cent Agreement
- Not Infected	103	102	1	99.0%
+1 Not Infected	59	54	5	91.5%
- & +1 Totals	162	156	6	96.3%
+2 ?? Infected	30	21	9	30.0%
+3 Infected	25	14	11	44.0%
+4 Infected	39	16	23	59.0%
+3 & +4 Totals	64	30	34	53.1%

OVERALL AGREEMENT 199/256= 77.7% To #6171

* In collaboration with: DORSEY L. KORDICK, Ph.D., EDWARD B. BREITSCHWERDT, D.V.M. Department of Companion Animal and Special Species Medicine, College of Veterinary Medicine, North Carolina State University, Raleigh, North Carolina

Serologic Tests:

Compared to culture isolation of *Bartonella,* which requires special laboratories and 4 to 6 weeks of incubation, serologic tests have the advantage of ease of use, take only 1-2 days, and are economical. Infected cats produce specific antibodies against the bacterial proteins and the antibodies are an amplification system indicating the presence of the bacteria. The presence of antibodies indicates, in most instances, current active *Bartonella* infection and not a past history of infection. We have developed a specific and sensitive western immunoblot test for detection of antibodies against all species of *Bartonella* that infect cats and dogs (Figures 2 & 3 and Table 2). We have found the western immunoblot test correlates better with the isolation of *Bartonella* from cats than do the IFA or

ELISA *Bartonella* antibody tests.[57]

Bartonella infected cats produce antibody to as many as 14 bacterial proteins.[49,57] We have defined 9 immunodominant proteins of feline *Bartonella* and have developed a grading system for correlation of western immunoblot reactivity with *Bartonella* infection (Table 2). There is a high degree of serologic cross-reactivity between all the *Bartonella*, and the Fe*Bart*® immunoblot test will detect all feline *Bartonella* infections in cats. Western immunoblot test results of +3 and +4 are considered positive (Figure 2, 3 & 4) and these cats are considered to be actively infected with *Bartonella* and should be treated. Following antibiotic therapy we recommend the Western blot antibody titration test, 6 months after the completion of therapy to determine if there is a decrease in antibody titer indicating successful elimination of *Bartonella*.[61] **It is necessary to wait 6 months from the end of therapy in order to allow the antibody level to drop (catabolism) after removal of the *Bartonella* antigenic stimulation.** A 2 to 4 fold decrease in antibody titer indicates successful *Bartonella* therapy, however, another course of antibiotic therapy is recommended if the antibody titer does not decrease. Occasionally *Bartonella* can be isolated from cats who do not produce antibody and are seronegative by all tests (Table 1).[107]

Table 2
IMMUNOBLOT GRADING FOR ANTIBODIES TO *BARTONELLA* [57]

Grade	Reactivity	Infection	Treatment Recommended
+4	Very Strong	Infected	Yes
+3	Strong	Infected	Yes
+2	Fair	Possibly Infected	Yes/No*
+1	Weak	Uninfected	No
-	Negative	Uninfected	No

* Treat if healthy cat lives with young children or an immunosuppressed person or if cat has a *Bartonella*-associated disease.

Figure 2
FeBart® Test Immunoblot Grading

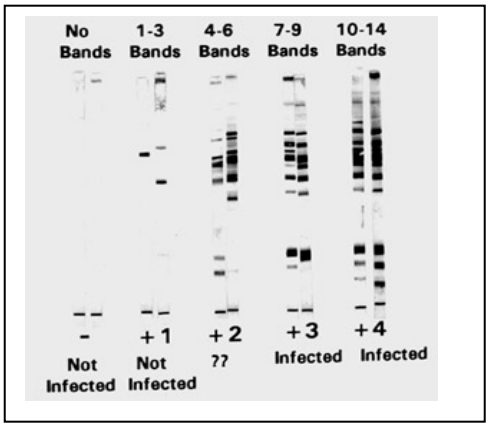
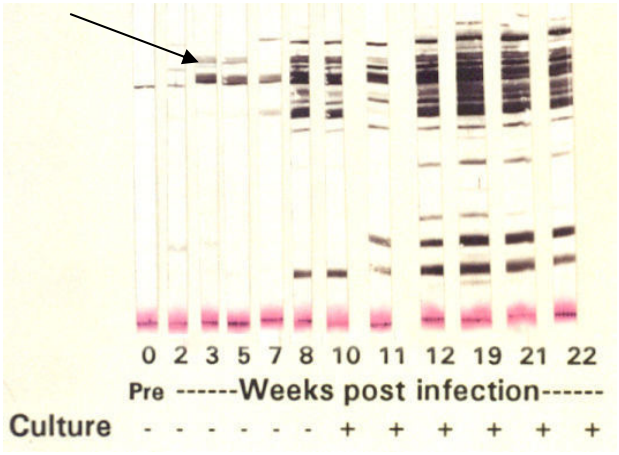


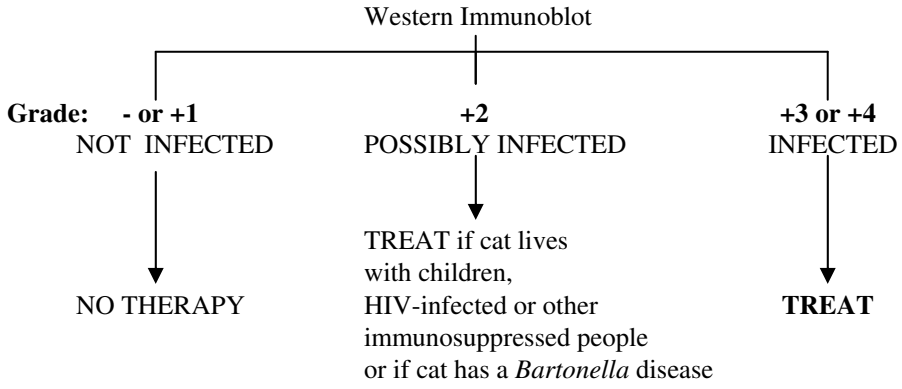
Figure 3 **SEROCONVERSION OF A CAT INFECTED BY BLOOD DONATION WITH *B. HENSELAE***



Legend: Antibody bands against *Bartonella* proteins develop by week 3 (arrow) after infection and progress to the full profile of antibodies to 14 proteins. *Bartonella* could be isolated from the blood at week 10 and beyond. Azithromycin therapy successfully cleared the bacteremia.

Figure 4

***BARTONELLA* SEROLOGY ALGORITHM**



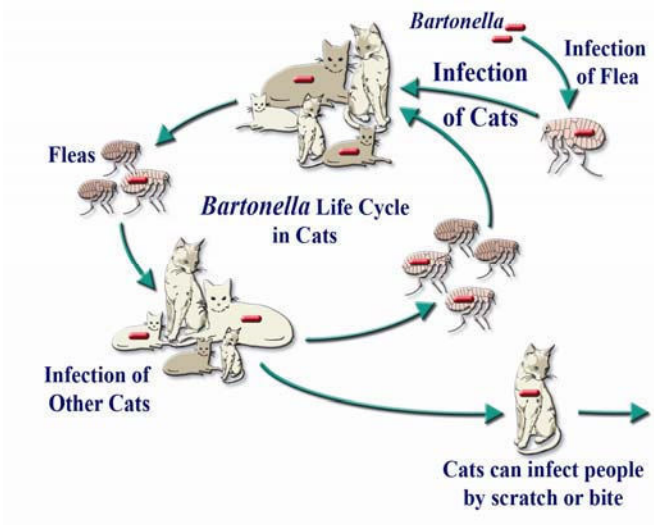
Prevalence of *Bartonella* Infection in Cats:

Healthy pet cats can carry five *Bartonella* species: *Bartonella henselae*, *Bartonella clarridgeiae*, *Bartonella koehlerae* *Bartonella elizabethae* and *Bartonella weissii*, in their blood. Most infected cats are healthy, inapparent carriers of these bacteria for years. It is not known if infected cats can clear their *Bartonella* infections or if they remain infected for life. Cat fleas and ticks spread the bacteria among cats and probably can occasionally transmit the bacteria to people. *B. henselae* is the major pathogenic *Bartonella* species infecting pet cats who serve as the major natural reservoir of this zoonotic pathogen. The prevalence of *Bartonella* infection varies in different regions of the United States and parallels increasing climatic warmth and annual precipitation (Figure 5 & Table 3).[32,33,60,68,71] Warm, humid areas have the highest *Bartonella* prevalence since they have the highest number of potential arthropod vectors such as fleas and ticks.[43,45,47,111,127] The Southeastern states, Hawaii, costal California, the Pacific Northwest, and the south central plains have the highest incidence whereas the Rocky Mountain and Great Plains states have the lowest prevalence (Figure 6). The heavily populated Northeast is a moderate prevalence area. The prevalence in cats living in Europe and Australia is similar to cats living in this country.[16,17,19]

Fleas transmit *Bartonella* from cat to cat and even to people.

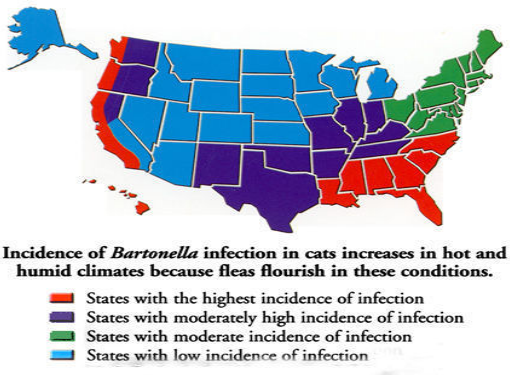
Figure 5

Cats and *Bartonella*



Prevalence of *Bartonella* in Healthy Cats in the USA[57,71]

Figure 6



Incidence of *Bartonella* infection in cats increases in hot and humid climates because fleas flourish in these conditions.

States with the highest incidence of infection
States with moderately high incidence of infection
States with moderate incidence of infection
States with low incidence of infection

Table 3

Healthy: No Reported Risk Factors	% Infected
Region 1: Southeast & Pacific Coast	28%
Red High Prevalence	
Regions 2: SW & Midwest	22%
Dk Blue Moderate High Prevalence	
Region 3: Northeast	17%
Green Moderate Prevalence	
Region 4: Rocky Mts, Great Plains & West	7%
Lt Blue Low Prevalence	
USA Totals:	**20%**

Risk Factors for *Bartonella* Infection in Cats:

Bartonella infection is significantly higher in stray cats, cats adopted from shelters or rescue organizations, cats living in multi cat households, and cats exposed to *Bartonella*-infected cats in multi cat households (Table 4).[48,60,64] The reason for the higher infection prevalence is due to an increased infestation with fleas compared to cats living in single cat households. Cats from these backgrounds are at greater risk for various infectious agents including FeLV, FIV, and *Bartonella*. We tested 53,406 cats for *Bartonella* infection, 42,591 of which had at least one known risk factor (many cats had several risk factors) from throughout the USA (Table 4). Of these, 20,766 (49%) were positive. The prevalence of infection is 3 times higher for cats with these risk factors than for cats with no known risk factors who live in single-cat households.

Table 4

Risk Factors for *Bartonella* Infection	All Cats with Known Risk Factors: *Bartonella* Incidence- USA:			Healthy Cats in Single-Cat Households
		% Infected		
Stray cats	Stray cats	4,349/8,947	**49%**	**Non-exposed healthy cats 69/470 16%**
Shelter cats	Shelter cats	2,831/6,636	**43%**	
Fleas- Present or past	Fleas- Present or past	4,018/7,044	**57%**	
Exposed healthy cats living in multi-cat households with other *Bartonella* infected cats	Living in multi cat households	8,254/17,624	**47%**	
	Living with *Bartonella* infected cat	1,314/2,340	**56%**	
Cats with flea infestation or history of fleas	**Totals:**	**20,766/42,591**	**49%**	

***BARTONELLA* DISEASES:**

Bartonella infects many species from rodents, carnivores, and ruminants to various primates including humans. Infection is silent in many species but diseases can occur in the reservoir hosts as well as incidental recipients of cross species transmission. It is becoming apparent that cats, who are the reservoir host for at least 5 *Bartonella* species, develop chronic inflammatory diseases due to their long duration of bacteremia. Dogs also carry a *Bartonella* and develop chronic inflammatory diseases as well. The most frequently occurring human *Bartonella*-induced disease is cat scratch disease which is caused by at least 2 *Bartonella* species.[56b,89,103,104,113,130,134,138,145] *Bartonella quintana*, the louse-borne agent of trench fever, was responsible for high morbidity among Allied and Axis troops in France in World War I.[27] Although rarely reported since the war, *Bartonella quintana* has been found as an opportunistic pathogen among immunocompromised people in the US within the past few years and in homeless people with endocarditis.[42,65,70,95,133] *Bartonella elizabethae* has recently been identified as a new member of the group and was isolated from people with endocarditis as well as cats in Sweden.[36] *Bartonella vinsonii*, which has been isolated from a vole on an island in the St. Lawrence River and recently dogs with endocarditis, has also been associated with human endocarditis.[21,22]

The list of *Bartonella* diseases in cats and humans is increasing rapidly (Table 5). *Bartonella henselae* and *Bartonella clarridgeiae* have been shown to cause cat scratch disease.[56b,89,103,104,113,130,134,138,145] Although named for its association with exposure to cats, the transmission of these bacteria from cats to humans has not been studied in detail until recently. In 1994 an important study was published which described the finding that the pet cat serves as a reservoir and the cat flea as vector(s) for *Bartonella henselae*.[75] Cat scratch disease affects an estimated 22,000 people annually, resulting in 2,000 hospitalizations, in the United States and many cases go

undiagnosed or misdiagnosed each year because of atypical clinical presentations.[119,122]

Bartonella henselae and *Bartonella quintana* have been found in immunocompromised patients with AIDS.[31,59,76-78,105,115,126,141] These bacteria cause significant illnesses and some mortality in AIDS patients and both are probably present in many more patients infected with HIV-1 than we know. More recently *Bartonella quintana* has been found to cause endocarditis in homeless inner city men.[27,42,133] Both bacteria are most likely transmitted by arthropod vectors from natural animal reservoirs to humans, cat fleas for *B. henselae* and body lice for *B. quintana*. Thus mites, lice, ticks and fleas may be important in spreading these pathogens. The increasing occurrence of both of these bacteria in the inner cities may be due to the increase in poverty and homelessness, which increases the likelihood of arthropod vectors in these populations due to poor personal hygiene. It will be important to determine the extent of infection with these bacteria in HIV-1 infected individuals in order to determine the true significance of these pathogenic agents. Relapsing fevers, malaise, bacillary angiomatosis, bacillary peliosis hepatis are associated with infections of these bacteria in AIDS patients whereas cat scratch disease, and 21 other *Bartonella* diseases, occur in immunocompetent people. Prompt treatment with antibiotics is important in people infected with *Bartonella*, especially in people of the inner city who have higher incidences of HIV and HTLV-I/II infections than people living elsewhere. Present research is aimed at identifying *Bartonella*-infected animals (cats and dogs) and people so that appropriate measures can be instituted to prevent infection of susceptible people from infected "carrier" animals and to treat people who are infected with these bacteria.

Table 5

***BARTONELLA* DISEASES IN HUMANS AND ANIMALS**

Feline *Bartonella* Diseases:	**Human *Bartonella* Diseases**
Oral Disease:	**Previously Described Diseases:**
Gingivitis	Cat Scratch Disease
Stomatitis	Bacillary angiomatosis
Oral Ulcers	Bacillary peliosis
Submandibular lymphadenopathy	Febrile bacteremia
Respiratory Diseases:	Endocarditis
URI	Vegetative valvular disease
Rhinitis	Uveitis
Sinusitis	Neurological disorders
Ocular Disease:	Anemia
Uveitis	Neuroretinitis
Chorioretinitis	Osteomyelitis
Conjunctivitis	AIDS encephalitis
Intestinal Diseases:	Trench Fever
Inflammatory bowel disease	Oroyo Fever
Diarrhea (chronic)	**Newly Described Diseases:**
Vomiting (chronic)	Inflammatory bowel disease
Skin Diseases:	Mononucleosis-like syndrome
Dermatitis	Pulmonary infiltrates
Papules- “acne”	Meningoencephalitis
Granulomas	Lymphadenopathy
Other Diseases:	Arthralgia
Lymphadenopathy	Juvenile arthritis
Fever of unknown origin	Cutaneous rash- Henoch Schenlein purpura
Liver Diseases	Cutaneous granuloma annulare
Heart Diseases	Disciform keratitis
	Co-infection with Lyme disease

Cat *Bartonella* Diseases:

The feline *Bartonella* appear to be moderately pathogenic for cats.[57,60,81,83,84] However, most *Bartonella* infected pet cats show no clinical signs of their infections.[32,33,53,57,71,75,111,141] *Bartonella* adhere to endothelial cells in highly vascular tissues such as the oral cavity, respiratory membranes, gastrointestinal tract and ocular tissues where they induce chronic lymphocytic-plasmacytic inflammation.[13,37,38,50,66,87,88,146] We have found that several **chronic** insidious diseases (Table 5) such as gingivitis, stomatitis and oral ulcers, upper respiratory infections including conjunctivitis, sinusitis and rhinitis, generalized painless lymphadenopathy, persistent fevers, uveitis, skin diseases, and chronic GI problems such as inflammatory bowel disease, chronic vomiting and diarrhea have been observed in *Bartonella*-infected pet cats under natural conditions. Transient neurological dysfunction and other abnormalities have also

been observed in experimentally infected cats.[1,54,55,56,94,99,143,144]

Bartonella Pathogenesis:

Feline *Bartonella* are Gram-negative bacilli that possess pili which are hair-like structures found on the bacteria's surface. *Bartonella* have a strong tendency to stick or clump together in tissues and in culture and to stick to, and penetrate, RBCs and endothelial cells.[13,37,38,50,66,87,88,93,104,118,124,142a,146] The ability to adhere to each other, and to the membranes of RBCs and endothelial cells, leads to the wide and varied tissue pathogenesis observed in cats, dogs and people. Pili and a protein called deformin are probably responsible for the sticky properties.[142a] The wide tissue specificity of *Bartonella* is due to the adhesion to endothelial cells which are the constituents of capillaries. Experimental data show that B. *henselae* interaction with macrophages induces potential angiogenic growth factors (vascular endothelial growth factor- VEGF and interluken-1beta- IL-1beta) which, through a paracrine mechanism, induce proliferation of endothelial cells.[118] *Bartonella* proteins stimulate endothelial cells (Figure 7) to proliferate causing neovascularization or angiogenesis and an outpouring of inflammatory cytokines which recruit inflammatory cells such as lymphocytes, plasma cells and macrophages. Thus, *Bartonella* induce chronic lymphocytic plasmacytic granulomatous inflammatory reactions in highly vascular tissues throughout the infected animal's body. These tissues are: oral and respiratory mucosa, ocular tissues, the gastro-intestinal tissues, the skin, and organs such as the liver, spleen and lymph nodes. In fact, since capillaries are found in all tissues, all tissues are susceptible to the inflammatory effects of *Bartonella*. The tissue reactions are apparent in the mucosa of the mouth, eye and respiratory tract or evidenced in the GI tract by chronic vomiting or diarrhea.

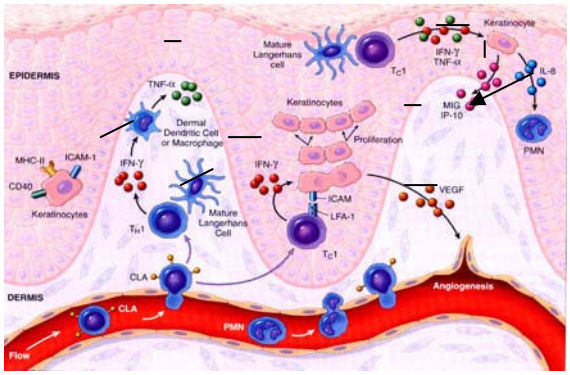


Figure 7 *Bartonella* Inflammation

The black rods (--) represent *Bartonella* in the skin or mucosa. The bacteria induce angiogenesis (arrow) and an outpouring of inflammatory cytokines, which recruit inflammatory cells such as lymphocytes, plasma cells and macrophages.

Baseline *Bartonella* Prevalence in Healthy Cats:

In order to establish a baseline prevalence of *Bartonella* infection in healthy cats we tested 53,406 pet cats from throughout the US, Caribbean and Canada for *Bartonella* infection using a western immunoblot antibody assay developed in our laboratory, the Fe*Bart*® test.[60,62] There were 13,953 healthy cats with *Bartonella*-type inflammatory diseases, 1,082 cats with possible *Bartonella*-type diseases, 523 cats with non-*Bartonella*-type diseases, 621 cats with miscellaneous diseases, and 1,673 cats where no diagnosis was available (Table 6). *Bartonella* infected cats often have several inflammatory diseases in various sites. For our analysis, each cat was assigned one risk factor or a single primary disease (Table 6-15). In contrast, the data in the Tables for the healthy cats with infection risk factors and for cats with various diseases represent data for each risk or disease category and the totals exceed the number of cats in the study since many cats had multiple risk factors and or multiple diseases

In our initial survey of cats living in New Jersey suburbs, the owners of 840 healthy cats did not report any infection risk factors (Table 7). 170 of the 840 (20%) healthy cats without known risk factors were seropositive and this prevalence is used as the baseline prevalence to judge increased or decreased association of *Bartonella* infection with various feline diseases**.** In contrast, healthy cats with known risk factors for infection (strays, shelter cats, cats living in multi cat households and cats living with *Bartonella*-infected cats) (5,460+/13,953 tested) were about twice as likely to be infected (Table 7).

Table 6 ***Bartonella* Infection in 53,406 Cats (To 8/1/04)**

Risk Factors	No. Tested	No. Positive	% Positive	Difference
HEALTHY- NO KNOWN RISK FACTORS	**840**	**170**	**20%**	**X**
ALL HEATHY CATS	**13,953**	**5,460**	**39%**	**1.9X**
Bartonella-type diseases*	**35,554**	**16,999**	**48%**	**2.4X**
Possible *Bartonella*-type disease	**1,082**	**499**	**46%**	**2.3X**
Non-*Bartonella*-type diseases	**523**	**231**	**44%**	**2.2X**
Miscellaneous Diseases	**621**	**268**	**43%**	**2.2X**
No diagnosis available	**1,673**	**734**	**44%**	**2.2X**
Totals:	**53,406**	**24,191**	**46%**	**2.3X**

* See Table 8 for *Bartonella* diseases

Table 7 ***Bartonella*** **and Known Risk Factors for Infection in Healthy Cats***

Risk Factors	No. Tested	No. Positive	% Positive	Difference
HEALTHY- NO KNOWN RISK FACTORS	**840**	**170**	**20%**	**X**
Unknown risk factors	**3,376**	**1,085**	**32%**	**1.6X**
Stray Cats	**3,355**	**1,358**	**41%**	**2.0X**
Shelter Cats	**2,089**	**725**	**35%**	**1.8X**
Flea infestation or history of fleas	**1,866**	**957**	**51%**	**2.6X**
Cats living in Multi Cat Households	**5,170**	**8,254**	**44%**	**2.2X**
Exposed cats- living with a *Bartonella* infected cat	**1,327**	**712**	**54%**	**2.7X**
Cats with Known Risk Factors- Totals:	**13,807**	**6,017**	**44%**	**2.2X**

* Totals do not equal total number of cats tested since many cats had multiple risk factors.

Risk Factors in Different Breeds of Cats:

Of the 53,404 cats in our study, 46,484 were domestic short-haired (DSH) cats, 314 cats had no breed listed, and the remaining 6,613 were pure breeds: Siamese, Persian, Himalayan, Maine Coon, Abyssinian, Russian Blue, Scottish Fold, Ragdoll, Burmese, Tonkinese, and several other breeds. There were a total of 13,953 healthy cats: 12,735 healthy DSH cats, 1,152 healthy pure breed cats and 66 cats of unknown breed were tested for *Bartonella* infection (Table 8). Unlike the DSH cats in our study, most of the pure breed cats had not been strays and had not come from shelters, both of which are major risk factors for *Bartonella* infection. However, some were living in multi cat households, lived in households (exposed) with *Bartonella* infected cats and had histories of flea infestations. Thus there was a significant reduction in the risk factors for infection for pure breed cats. The analysis of the *Bartonella*-infection prevalence in healthy pure bred cats with no known risks of infection found that the overall infection incidence was only 15% 0.75X (57/376) whereas the incidence of infection for DSHs with no known risk factors was 34% 1.7X (1,024/2,987). The difference was 2.3X less for purebred cats which reflected their "cleaner" backgrounds compared to DSHs.

Table 8 ***Bartonella*** **Infection in Healthy Cats: Analyzed by Breeds***

Risk Factors	No. Tested	No. Positive	% Positive	Difference
HEALTHY- ALL BREEDS: NO KNOWN RISK FACTORS	**840**	**170**	**20%**	**X**
DSHs				
Healthy- with NO Known Risk Factors	**2,987**	**1,024**	**34%**	**1.7X**
Healthy- WITH Risk Factors	**9,746**	**4,128**	**42%**	**2.1X**
Totals:	**12,735**	**5,152**	**41%**	**2.1X**
Pure Breed Cats				
Healthy- with NO Known Risk Factors	**376**	**57**	**15%**	**0.75X**
Healthy- WITH Risk Factors	**776**	**223**	**29%**	**1.5X**
Totals:	**1,152**	**280**	**24%**	**1.2X**
Grand Totals:	**13,885***	**5,432**	**39%**	**1.9X**

* 66 healthy cats were tested but no breed was identified.

Prevalence of *Bartonella* Infection in Cats with Chronic Inflammatory Diseases:

After the first identification of *Bartonella* in human tissues, *Bartonella* diseases were first recognized in humans. The cat was recognized as the natural host for these bacteria but early investigations concluded that *Bartonella* were not pathogenic in their natural host. We assumed that *Bartonella* might be pathogenic in some cats and began a systematic search, with hundreds of veterinary practitioners, for any association of *Bartonella* in cat diseases which were similar to those already described in humans.[29,30,69,92]

In order to establish a baseline prevalence of *Bartonella* infected cats with inflammatory diseases, as of August 1, 2004, we have tested 53,406 pet cats from throughout the US, Caribbean and Canada for *Bartonella* infection.[60,62,Unpublished data] *Bartonella* infected cats often have several inflammatory diseases in various sites. For our analysis, each cat was assigned one risk factor or their primary disease for Table 9. In contrast, the data in the Tables for the healthy cats with defined infection risk factors and for cats with various diseases represent data for each risk or disease category. The totals exceed the number of cats in the study since many cats had multiple diseases, ie. gingivitis and URI, uveitis and dermatitis, gingivitis, inflammatory bowel disease and

cholangiohepatitis, etc. Some cats in our study had as many as 6 inflammatory diseases in various organ systems.

Table 9

Bartonella in Cats with Chronic Inflammatory Diseases

Disease	No. Tested	No. Positive	% Positive	Difference
HEALTHY- NO KNOWN RISK FACTORS	**840**	**170**	**20%**	**X**
Oral Diseases	**22,934**	**10,996**	**48%**	**2.4X**
Respiratory Diseases	**5,516**	**2,661**	**48%**	**2.4X**
Ocular Diseases	**3,324**	**1,572**	**47%**	**2.4X**
GI Diseases	**1,550**	**721**	**47%**	**2.4X**
Skin Diseases	**636**	**306**	**48%**	**2.4X**
Other *Bartonella* Diseases	**1,594**	**743**	**47%**	**2.4X**
***Bartonella* Disease Totals:**	**35,554**	**16,999**	**48%**	**2.4X**
Possible *Bartonella* Diseases	**1,082**	**499**	**46%**	**2.3X**
Non-*Bartonella* Diseases	**2,196**	**965**	**44%**	**2.2X**
Grand Totals:	**38,832**	**18,463**	**48%**	**2.4X**

As can be seen from the data in Table 9, cats with chronic inflammatory disease in various organ systems are more than twice as likely to be seropositive for *Bartonella* antibody compared to healthy cats with no known risk factors for infection. About 48% of cats with these chronic inflammatory diseases are infected. Additional evidence for the *Bartonella* etiology for these diseases comes from the response to *Bartonella* therapy with the corresponding decrease in *Bartonella* antibody titers (see the section on *Bartonella* disease therapy).

Oral Inflammatory Diseases:

Gingivitis, stomatitis and oral ulcers are common and often perplexing problems caused by numerous viral, bacterial and fungal microbial pathogens. There is ample serological evidence that a subset of each of these diseases is caused by systemic infection with *Bartonella* (Table 10). However, it is likely that *Bartonella*-infected cats with oral disease are also infected with other pathogenic micoorganisms and that the diseases are probably polymicrobial diseases.[25]

Table 10

Bartonella in Cats with Oral Disease*

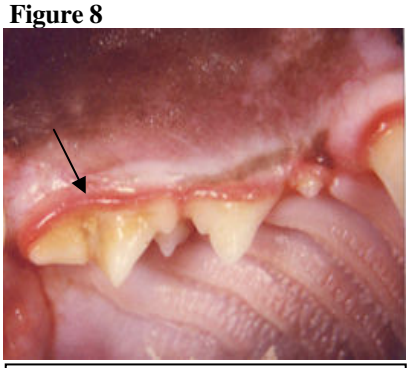
Oral Disease	No. Tested	No. Positive	% Positive	Difference
HEALTHY- NO KNOWN RISK FACTORS	**840**	**170**	**20%**	**X**
Gingivitis	**21,338**	**10,107**	**48%**	**2.4X**
Stomatitis	**1,350**	**760**	**56%**	**2.8X**
Oral Ulcers	**246**	**129**	**52%**	**2.6X**
Oral Disease Totals:	**22,934**	**10,996**	**48%**	**2.4X**

* Totals do not equal total number of cats tested since many cats had multiple inflammatory diseases.

We found 10,996 *Bartonella* seropositive cats of 22,934 (48%) cats with oral diseases (Table 10): gingivitis: 10,107/21,338 48%; stomatitis 760/1,350 56%; oral ulcers 129/246 52%. In contrast only 170 of 840 (20%) healthy cats, with no infection risk factors, were seropositive. Thus, cats with oral inflammatory diseases are 2.4 times more likely to be infected with *Bartonella* than healthy cats.

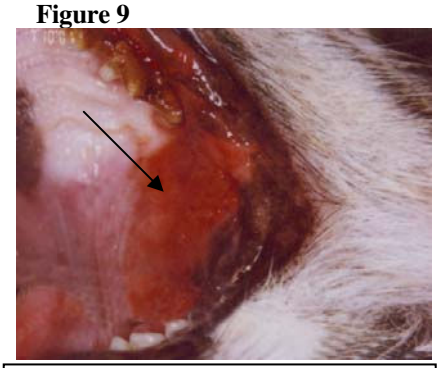
There is no distinct clinical or pathological presentation of *Bartonella*-seropositive oral diseases compared to oral diseases caused by other pathogens. Clinical parameters range from slight to very severe, including total mouth extractions (Figure 8, 9 & 10). The pathological parameters of *Bartonella*-seropositive cats with oral diseases also range from slight to severe inflammation, some with lymphocytic-plasmacytic inflammation. Veterinarians should consider *Bartonella*, in their differential diagnosis, as the etiological agent for a subset of cats with oral inflammatory disease. In this regard we have found azithromycin to be an effective therapy for more than 80% of cats with *Bartonella*-seropositive oral diseases (see therapy section), even in many cats where previous antibiotic and steroid therapy failed. In addition, veterinarians should be aware that *Bartonella*-infected cats with oral inflammatory diseases are more likely to transmit these dangerous bacteria to their owners (zoonosis) from their blood via blood and inflammatory fluids in the oral cavity than cats with healthy mouths.

Figure 8



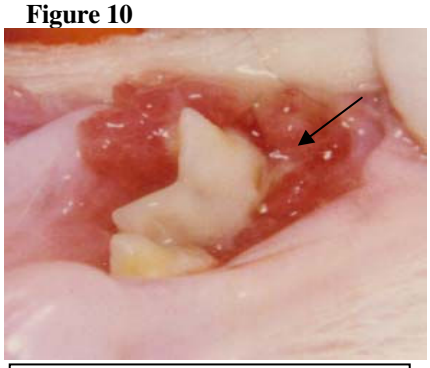
Gingivitis in a 6 month old cat with minimal tartar. This cat had a bacteremia of 1000 *Bartonella*/ml and was Fe*Bart* test +4

Figure 9



Chronic stomatitis in a cat that tested +3 by the Fe*Bart* test. The stomatitis was present for 3 years and resolved after azithromycin therapy.

Figure 10



Severe proliferative gingivitis in a Fe*Bart* test +3 cat with a history of flea infestation

Upper Respiratory Diseases:

We found 2,661 *Bartonella* seropositive cats of 5,516 (48%) cats with upper respiratory diseases (Figure 11 & Table 11): URI 3,519/7,192 49%; rhinitis (Figure 12) 400/729 55% and sinusitis 283/550 52%. Thus, cats with upper respiratory diseases are 2.5 times more likely to be infected with *Bartonella* than healthy cats.

Table 11

Bartonella in Cats with Upper Respiratory Disease*

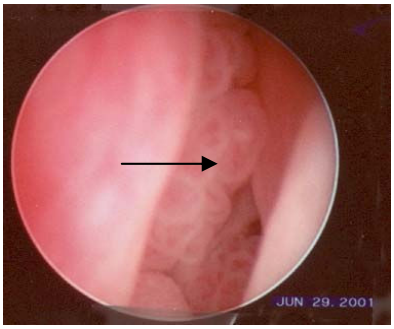
Upper Respiratory Disease	No. Tested	No. Positive	% Positive	Difference
HEALTHY- NO KNOWNRISK FACTORS	840	170	20%	X
URI	4,643	2,188	47%	2.4X
Rhinitis	643	357	56%	2.8X
Sinusitis	230	116	50%	2.5X
Upper Respiratory Disease Totals:	5,516	2,661	48%	2.4X

* Totals do not equal total number of cats tested since many cats had multiple inflammatory diseases.

Figure 11

Chronic URI

Figure 12



Rhinitis- chronic 1.5 years

Photographs courtesy of:

Jan Corbishley, B.S. Oradell Animal Hospital, Paramus, NJ: Chronic URI

Dr. Larry Kantrowitz, Oradell Animal Hospital, Paramus, NJ,
Currently Animal Emergency & Referral Center, West Caldwell, NJ: Rhinitis

Ocular Disease:

Ocular diseases are among the most common *Bartonella*-induced diseases in humans and cats.[60,62,73,83,84 & Bartonella Ocular References] We found 1,572 *Bartonella* seropositive cats of 3,324 (47%) cats with ocular diseases (Table 12): conjunctivitis 1,095/2,431 45%; uveitis 364/674 54%; chorioretinitis 16/28 57%; keratitis 33/74 45%; corneal ulcers 48/89 54%; glaucoma 3/5 60%; epiphora 11/17 65% and blepharitis 2/6 33%. Thus, cats with ocular diseases are 2.4 times more likely to be infected with *Bartonella* than healthy cats.[73]

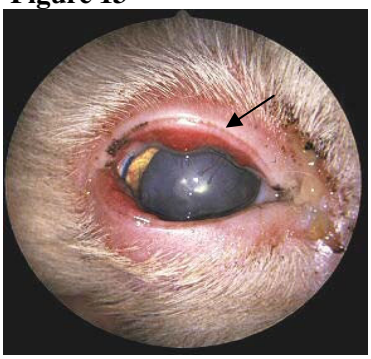
Table 12

Bartonella in Cats with Ocular Disease*

Ocular Disease	No. Tested	No. Positive	% Positive	Difference
HEALTHY- NO KNOWN RISK FACTORS	840	170	20%	X
Conjunctivitis	2,431	1,095	45%	2.3X
Uveitis	674	364	54%	2.7X
Chorioretinitis	28	16	57%	2.9X
Keratitis	74	33	45%	2.3X
Corneal Ulcer	89	48	54%	2.7X
Glaucoma	5	3	60%	3.0X
Epiphora	17	11	65%	3.3X
Blepharitis	6	2	33%	1.7X
Ocular Disease Totals:	3,324	1,572	47%	2.4X

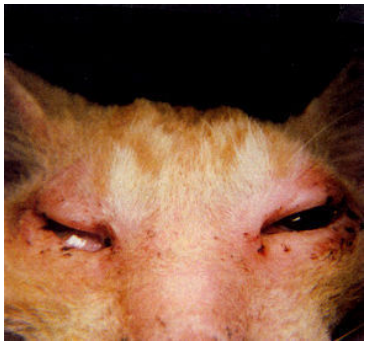
* Totals do not equal total number of cats tested since many cats had multiple inflammatory diseases.

Figure 13



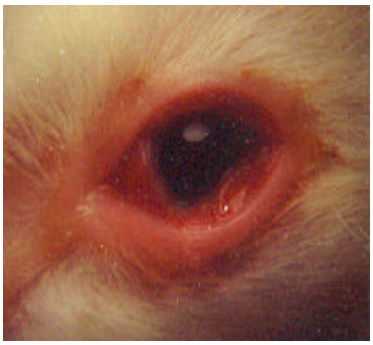
Uveitis & Blepharitis

Figure 14



Conjunctivitis & Blepharitis

Figure 15



Conjunctivitis

Figure 16

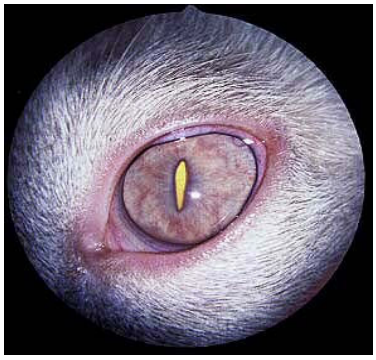


Figure 17

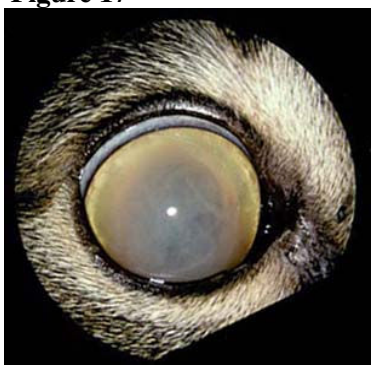
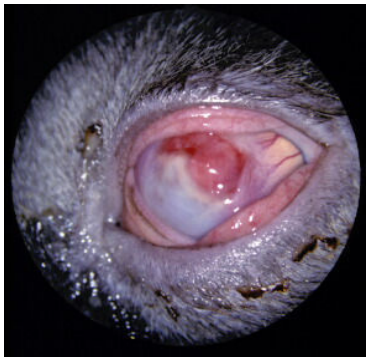


Figure 18



Photographs courtesy of:
Figures 13, 16, 17, 18: Dr. Kerry Ketring, All Animal Eye Clinic, Cincinnati, OH [73]
Figure 14: Dr. Jack Broadhurst, Cat Health Clinic, Pinehurst, NC

Figure 15 Chronic uveitis, blepharitis and facial dermatitis in an infected 15-year-old cat.
Figure 14 Chronic (6 years) conjunctivitis, blepharitis and facial dermatitis in an infected cat.
Figure 15 Severe chronic conjunctivitis in an infected 6-month-old kitten recently adopted from a shelter.
Figure 16 Anterior uveitis in a 5-month old infected Siamese cat. The iris is swollen and off-color.

Figure 17 A 15-year-old infected DSH cat with uveitis, corneal edema and a fibrous clot in the anterior chamber and pupil.
Figure 18 A 3-year-old infected DSH cat with chronic URI, blepharitis, chemosis, conjunctivitis and corneal ulcer.

Gastrointestinal Disease:

We found 721 *Bartonella* seropositive cats of 1,550 (47%) cats with gastrointestinal diseases (Table 13): inflammatory bowel disease 189/404 47%; chronic diarrhea 270/586 46%, and chronic vomiting 262/560 47%. Thus, cats with gastrointestinal diseases are 2.4 times more likely to be infected with *Bartonella* than healthy cats.

Table 13 ***Bartonella*** **in Cats with Gastrointestinal Disease***

Gastrointestinal Disease	No. Tested	No. Positive	% Positive	Difference
HEALTHY- NO KNOWN RISK FACTORS	840	170	20%	X
Inflammatory bowel disease	404	189	47%	2.4X
Diarrhea- chronic	586	270	46%	2.3X
Vomiting- chronic	560	262	47%	2.4X
Gastrointestinal Disease Totals:	1,550	721	47%	2.4X

* Totals do not equal total number of cats tested since many cats had multiple inflammatory diseases.

Skin Disease:

We found 306 *Bartonella* seropositive cats of 636 (48%) cats with skin diseases (Figures 19-21, Table 14): skin papules "acne" 90/182 50%, and granulomas 31/66 47%. Thus, cats with skin diseases are 2.4 times more likely to be infected with *Bartonella* than healthy cats. Feline *Bartonella* are known to cause several similar skin diseases in humans (Table 5).

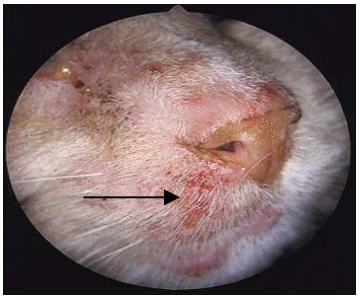


Figure 19
Left: Chronic facial rash (dermatitis) in a cat with chronic uveitis. The uveitis and facial skin rash resolved completely with azithromycin therapy.[11] **Dr. Kerry Ketring: All Animal Eye Clinic, Cincinnati, OH**

Figure 20
Right: Chronic chin papule "acne" in a young cat who also had gingivitis and chronic URI.

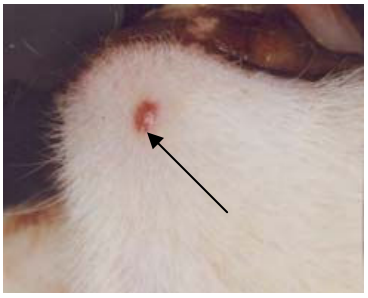


Table 14 ***Bartonella*** **in Cats with Skin Disease***

Skin Disease	No. Tested	No. Positive	% Positive	Difference
HEALTHY- NO KNOWN RISK FACTORS	840	170	20%	X
Dermatitis	388	185	48%	2.4X
Papules- "acne"	182	90	50%	2.5X
Granulomas	66	31	47%	2.4X
Gastrointestinal Disease Totals:	636	306	48%	2.4X

* Totals do not equal total number of cats tested since many cats had multiple inflammatory diseases.

Other *Bartonella*-Type Diseases:

All of the feline diseases summarized in Table 15 have first been shown to be caused by feline *Bartonella* in humans. We looked for similar diseases in pet cats and found 743 *Bartonella* seropositive cats of 1,594 (47%) cats with similar *Bartonella*-type other diseases: lymphadenopathy (Figure 22) 131/295 44%; fever of unknown origin 364/789 46%; heart disease (valvular & cardiomyopathy- HCM) 179/344 52% and liver disease 69/166 42%. Thus, cats with other *Bartonella*-type diseases are 2.4 times more likely to be infected with *Bartonella* than healthy cats.

Figure 22

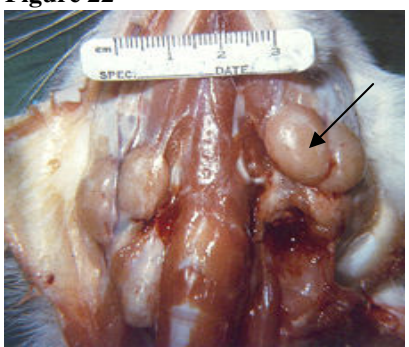


Figure 22
Left: Chronic lymphadenopathy in a stray cat that was Fe*Bart* test +4 and had a bacteremia of 400 *Bartonella* /ml.

Figure 21

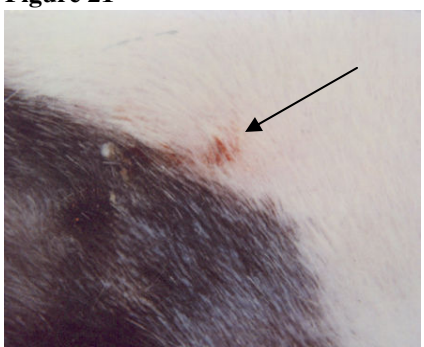


Figure 21

Right: Raised papule in the skin in a Fe*Bart* +4 cat. The cat had a bacteremia of 1000 *Bartonella*/ml and gingivitis

Table 15

Bartonella in Cats with Other *Bartonella* Type Diseases

Other Diseases	No. Tested	No. Positive	% Positive	Difference
HEALTHY- NO KNOWN RISK FACTORS	840	170	20%	X
Lymphadenopathy	295	131	44%	2.4X
Fever of unknown origin	789	364	46%	2.3X
Heart disease- Valvular & HCM	344	179	52%	2.6X
Liver Disease	166	69	42%	2.1X
Totals:	1,594	743	47%	2.4X

"Possible" *Bartonella*-Type Diseases:

The following "Possible *Bartonella*-Type" diseases of cats may be caused by *Bartonella* but more evidence is required. Similar diseases (anemia, polyarthritis, neurological syndromes and seizures) have been shown to be caused by feline *Bartonella* in humans and anemia and renal disease, have been shown to occur in cats experimentally infected with *Bartonella*.[4,56,89,94,99,104,110,113,130,134,] We found 499 *Bartonella* seropositive cats of 1,082 (46%) cats with "Possible *Bartonella*-Type" diseases (Table 16): anemia 166/341 49%; diabetes mellitus 224/479 47%; renal disease 36/83 41%; polyarthritis 14/31 45% and neurological syndromes 59/148 40%. Thus, cats with "Possible *Bartonella*-Type diseases are 2.3 times more likely to be infected with *Bartonella* than healthy cats.

Table 16

"Possible" *Bartonella* Diseases in Cats

Diseases	No. Tested	No. Positive	% Positive	Difference
HEALTHY- NO KNOWN RISK FACTORS	840	170	20%	X
Anemia	341	166	49%	2.5X
Diabetes Mellitus	479	224	47%	2.4X
Renal Disease	83	36	41%	2.1X
Polyarthritis	31	14	45%	2.3X
Neurological Syndromes	148	59	40%	2.0X
Totals:	1,082	499	46%	2.3X

Non-*Bartonella*-Type Diseases:

The following "Non-*Bartonella*-Type" diseases of cats are probably not caused by *Bartonella.* No similar diseases have been shown to be caused by feline *Bartonella* in humans or in experimentally infected cats.[94,99] We found 965 *Bartonella* seropositive cats of 2,196 (44%) cats with "Non-*Bartonella*-Type" diseases (Table 17): abscess 24/55 44%; asthma 37/97 38%; chylothorax & pleural effusion 5/20 25%; cystitis 15/31 48%; hyperthyroidism 16/26 62%; lethargic 7/29 24%; no diagnosis 734/1,673 44%; "sick" 15/29 52%; urinary tract infections 21/48 44%; weight loss 81/160 51%, and wounds 10/28 36%. Thus, cats with "Non- *Bartonella*-Type" diseases are 2.2 times more likely to be infected with *Bartonella* than healthy cats.

Table 17

Non- *Bartonella* –Type Diseases in Cats

Diseases	No. Tested	No. Positive	% Positive	Difference
HEALTHY- NO KNOWN RISK FACTORS	840	170	20%	X
Abscess	55	24	44%	2.2X
Asthma	97	37	38%	1.9X
Chylothorax & Pleural Effusion	20	5	25%	1.3X
Cystitis	31	15	48%	2.4X
Hyperthyroidism	26	16	62%	3.1X
Lethargic	29	7	24%	1.2X
No Diagnosis	1,673	734	44%	2.2X
"Sick"	29	15	52%	2.6X
Urinary Tract Infections	48	21	44%	2.2X

Weight Loss	**160**	**81**	**51%**	**2.5X**
Wounds- Chronic	**28**	**10**	**36%**	**1.8X**
Totals:	**2,196**	**965**	**44%**	**2.2X**

THERAPY:

Human therapy trials have shown that long-term azithromycin therapy is effective in shortening the course of CSD.[11,12,106,131] The treatment of *Bartonella*-infected sick or healthy cats requires commitment by the cat owner since the duration can be long and vigorous flea control is necessary. Treatment regimes have been found to be approximately 80% effective in eliminating the bacteria and resolving the *Bartonella*-induced clinical illnesses (Figures 23A, B, C, D & Figures 24A, B & Figure 25). Cat owners should be warned to avoid cat scratches and bites when treating their pets. We recommend azithromycin as the antibiotic of choice since it has proven to be effective and only requires 21 days of therapy. Doxycycline is as effective as azithromycin but requires a course of 6 weeks of therapy. Rifampin is as effective as azithromycin although there have been more reports of adverse reactions consisting of allergic reactions (red pruritic face and paws).[52,58,61,63,95,106,116,131] We recommend rifampin as the second antibiotic choice when azithromycin therapy has failed to eliminate *Bartonella*.

Antibiotics for *Bartonella* Therapy

Azithromycin: 10mg/kg daily for 21 days. **Treat for 21 days. Recommended first choice.**
Rifampin: 10mg.kg daily for 21 days Rifampin penetrates into RBCs where *Bartonella* are found.
Doxycycline: 10 mg/kg every 12 hours for 6 weeks.

AZITHROMYCIN THERAPY OF *BARTONELLA*-INFECTED CATS WITH GINGIVITIS AND STOMATITIS

Oral inflammatory diseases, gingivitis, stomatitis, and oral ulcers are common in pet cats and present a therapeutic challenge to veterinarians. Before effective therapy can be instituted, the cause of the oral disease should be determined. We have found an association of a subset of feline oral diseases with *Bartonella* infection and present data to support effective antibiotic therapy for most of these cases. The Macrolide azithromycin has been found to be effective in treating people with cat scratch disease and other *Bartonella*-induced diseases and we have adapted this therapy for *Bartonella*-infected cats.

Therapy:

We, in collaboration with numerous veterinarians around the US, have treated 254 *Bartonella*-seropositive cats with oral inflammatory diseases: gingivitis n=187, stomatitis n=64, and oral ulcers n=3. Treatment consisted of dental procedures as indicated and azithromycin 10mg/kg once daily for 10 days. Some cats received steroids when indicated for painful severe inflammation. No other antibiotics were given and cats were evaluated from 1 week to 2 years following completion of therapy. Therapy titration tests were performed for 82 cats that were treated and clinically evaluated. A decrease in *Bartonella* antibody titer of 2 fold or more indicates successful *Bartonella*-infection therapy.

Follow-up examinations were performed by collaborating veterinarians and the clinical data were transmitted to us via a standard evaluation form. The clinical response of the oral diseases was classified into 4 categories: 1) excellent= 80% to 100% improvement; 2) good= 60% to 80% improvement; 3) fair= 50% to 60% improvement and; 4) no-improvement= no or slight improvement. Many of the treated cats had been refractory to previous antibiotic (not azithromycin), steroid, and multiple extraction therapy.

Bartonella Therapy Alert

Diabetes Mellitus

It has come to our attention, through the very astute observations of Dr. Phillip Raclyn of the Riverside Veterinary Group, New York, NY and Yorktown Animal Hospital, Yorktown Heights, NY, that azithromycin therapy of *Bartonella* infected cats with diabetes mellitus may markedly alter the requirement for insulin maintenance. Dr. Raclyn has treated two *Bartonella*-infected diabetic cats (treated for other *Bartonella*-associated diseases) with 21 days of azithromycin and noted that one cat no longer required insulin to maintain a normal blood glucose level. The second cat went into a hypoglycemic coma while being treated with azithromycin. The cat recovered and presently requires significantly less insulin for blood glucose maintenance.

We theorize that *Bartonella* may be responsible for inducing inflammation of the pancreas in some cats resulting in diabetes mellitus. Thus, when azithromycin therapy removes the *Bartonella*-infection, and resulting pancreatic inflammation, the insulin controlled glucose metabolism can return to normal in some cats. In this regard we have checked our *Bartonella* Fe*Bart*® Test records and found that 63 of 123 (51%) cats with diabetes were infected. Most of these diabetic cats were being tested for another reason, such as gingivitis, URI or another *Bartonella*-associated inflammatory disease.

We are interested in testing diabetic cats to ascertain if a subset of cats with this disease are infected with *Bartonella*. Inflammation of the insulin producing tissues of the pancreas may cause malfunction resulting in inadequate insulin release and altered glucose metabolism. We would like to obtain follow-up information on azithromycin treated diabetic cats.

****RECOMMENDATION****

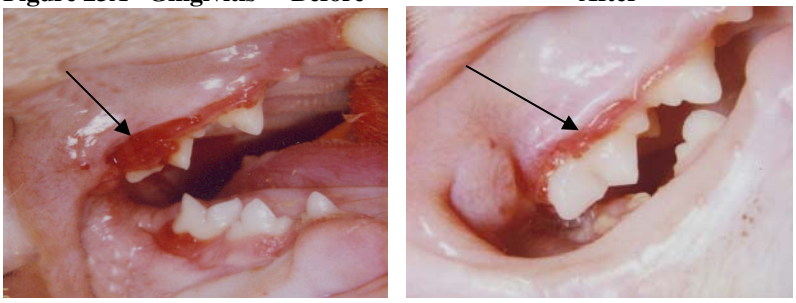
The blood glucose levels of *Bartonella*-infected diabetic cats, who are being maintained on insulin, should be monitored closely during azithromycin therapy. Alteration of the insulin maintenance dose may be required.

Clinical Therapy Results:

Gingivitis:

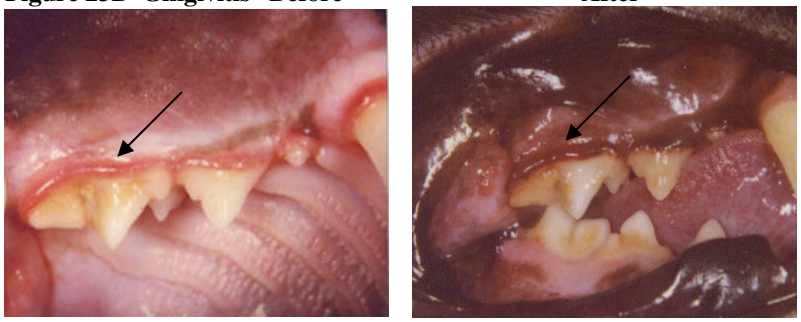
A total of 213 of the 254 (84%) treated cats with oral diseases showed a clinical improvement of 50% or greater.[58,61,63] Clinical improvement was observed in 167 of the 187 cats with gingivitis after azithromycin therapy: excellent response n= 124 (66%); good response n= 34 (18%) and fair response n= 9 (5%) whereas 20 (11%) cats did not improve with therapy.

Figure 23A Gingivitis Before **After**



Before:
Proliferative gingivitis in a Fe*Bart* +3 young cat with no tartar.
After: There was 75% resolution by 1 week and complete resolution by 4 weeks after azithromycin therapy.
Courtesy of: Jan Corbishley,
Oradell Animal Hospital,
Oradell, NJ.

Figure 23B Gingivitis Before **After**

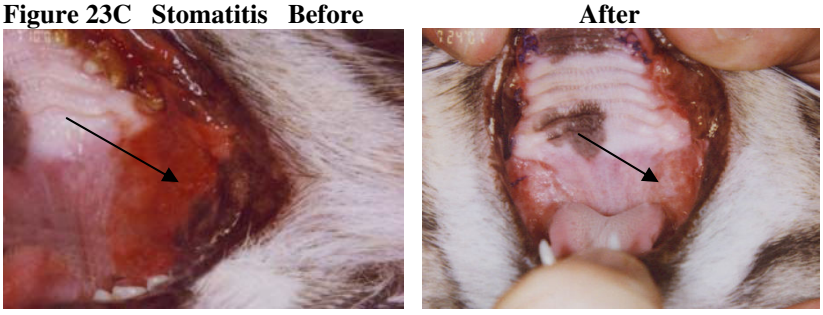


Before:
Gingivitis- 6 month old stray cat with fleas and minimal tartar. Fe*Bart* Test +4 strong positive. 1000 *Bartonella henselae* CFU/ml were isolated from the blood before therapy. Raised erythematous skin nodule also present
After: 2 years after therapy
Gingivitis and skin nodules completely resolved. No *Bartonella* were isolated from repeated blood cultures. The *Bartonella* titer decreased 4 fold from 1:512,000

Stomatitis:

The response rate was lower for the 64 cats with stomatitis. Only 68% of these cats improved more than 50% with therapy: excellent n=24 (38%); good n= 12 (19%); and fair n= 7 (11%).

Figure 23C Stomatitis Before **After**

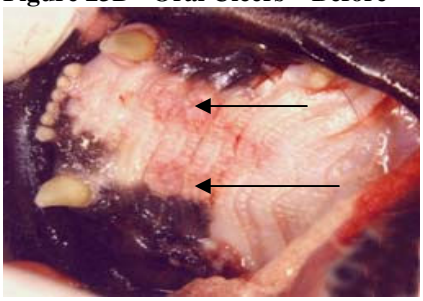


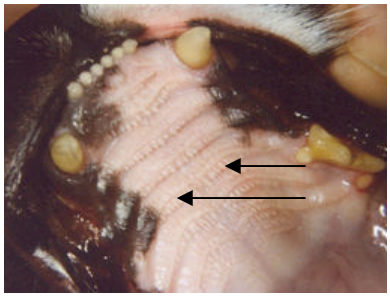
Before:
Stomatitis and gingivitis- 8 year old cat with severe tartar. Fe*Bart* Test +3. Dental prophy with multiple extractions performed and azithromycin therapy given.
After: 2 month after therapy
Stomatitis and gingivitis resolved 80%. By 6 months the stomatitis resolved completely. The *Bartonella* titer decreased 2 fold from 1:64,000 before therapy to

Oral Ulcers:

Only 3 cats with oral ulcers were treated. All 3 cats improved clinically: excellent n= 1 (33%); and good n=2 (67%).

Figure 23D Oral Ulcers Before **After**





Before:
Oral Ulcers- 3 year old cat with mild dental disease.
Painful mouth, was dropping food when eating.
Fe*Bart* Test +3.
Dental prophy and azithromycin therapy given.

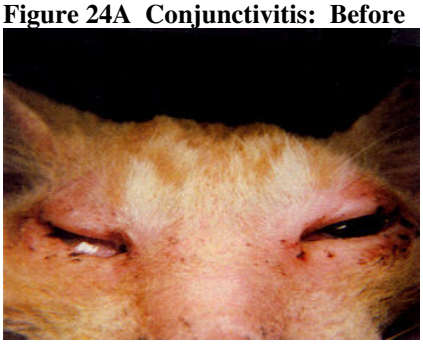
After: 3 month after therapy
Oral Ulcers completely resolved.

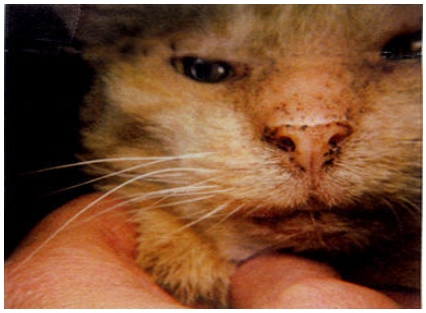
Other Disease:

Conjunctivitis:

All 8 cats with conjunctivitis to date, had an excellent complete resolution of their disease with azithromycin therapy.

Figure 24A Conjunctivitis: Before **After**





Conjunctivitis/Blepharitis
Severe chronic conjunctivitis, lasting for 6 years, before therapy (left) in a Fe*Bart* +4 cat. There was dramatic resolution of the conjunctivitis by the 7th day of therapy (right). Owner reported the cat was able to open its eyes for the first time in years.
Courtesy of:
Dr. Jack Broadhurst,
Cat Health Clinic, Pinehurst, NC.

Upper Respiratory Infection:

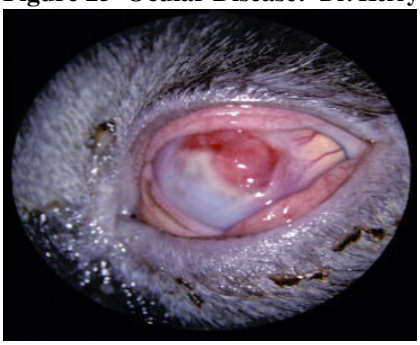
A total of 45 of the 47 (98%) treated cats with upper respiratory infections showed a clinical improvement of 50% or greater. Clinical improvement was observed in 98% of the treated cats: excellent response n= 42 (90%); good response n= 2 (4%); fair response n=2 (4%) whereas 1 cat (2%) did not improve with therapy.

Figure 24B URI: Before **After**

Upper Respiratory Infection

Before:
Chronic URI- mucopurulent nasal discharge.
Fe*Bart* Test +3 infected.
Treated with azithromycin
After:
Complete resolution of the URI by 2 weeks.

Figure 25 Ocular Disease: Dr. Kerry Ketring: All Animal Eye Clinic, Cincinnati, OH



Uveitis & Corneal Ulcer[73]
Before:
3 yr. old DSH- 6 weeks duration of URI, blepharospasms, chemosis, conjunctivitis, corneal ulcer. Fe*Bart* Test +4 infected.
Treated with azithromycin
After:
Complete resolution 2 months after therapy with azithromycin, topical antibiotics, and corticosteroids.

Bartonella Therapy Titration Results:

Bartonella western immunoblot antibody therapy titrations were performed for 82 treated cats: gingivitis n=72, stomatitis n=10.

Gingivitis:

Bartonella western immunoblot antibody therapy titrations were performed for 72 of the 187 treated cats with gingivitis. 69 of these 72 cats had a clinical improvement after azithromycin therapy. Of the 69 cats with gingivitis that showed clinical improvement 56 (81%) also had a 2 fold or greater decrease in their *Bartonella* antibody titers. In addition, 2 of the 3 cats, that did not improve clinically, also had a 2 fold or greater decrease in their *Bartonella* antibody titers.

Stomatitis:

Bartonella western immunoblot antibody therapy titrations were performed for 10 of the 64 cats with stomatitis. Nine of these 10 cats had a clinical improvement and 7 of 9 (78%) had a 2 fold or greater decrease in their *Bartonella* antibody titers. One stomatitis that did not improve clinically did not show a decrease in its *Bartonella* antibody titer.

Discussion:

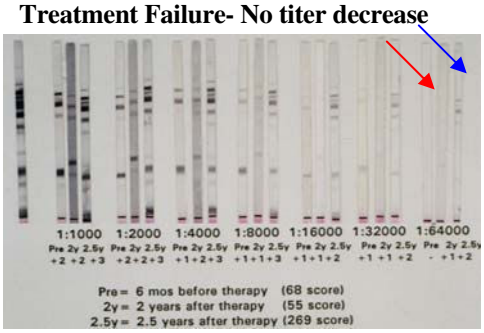
In general, there was a 2 fold or greater decrease in *Bartonella* antibody titers in about 80% of cats treated with azithromycin who clinically improved (Figure 26).[61,63] Some cats, who clinically improved had no decrease in their *Bartonella* antibody titers whereas, some cats, with marked decreases in their *Bartonella* antibody titers showed no clinical improvement with azithromycin therapy. These observations may be explained by the assumption that there are multiple microbial pathogens in some of these cats with oral disease and that therapy for one agent, *Bartonella*, is not curative in those cases. In the cases where there is a clinical cure with azithromycin therapy it can be assumed that *Bartonella* was the sole etiological agent.

Evaluation of Therapy:

Veterinarians may wish to evaluate the effectiveness of *Bartonella* therapy, especially in healthy cats, since the expected success rate for antibiotic therapy is ~80%. We recommend titration of the pre-treatment serum and comparison to a six-month post treatment serum.[61,63,116] Antibody titer of a pre-treatment serum sample can be compared with serum collected 6 months after completion of therapy. A 2 fold or greater decrease in *Bartonella* antibody titer, by the western immunoblot titration test, indicates successful reduction or removal of the *Bartonella* infection (Figure 26). **It is necessary to wait 6 months from the end of therapy in order to allow the antibody level to drop (catabolism) after removal of the *Bartonella* antigenic stimulation.** Those cats that fail the initial therapy should be retreated.

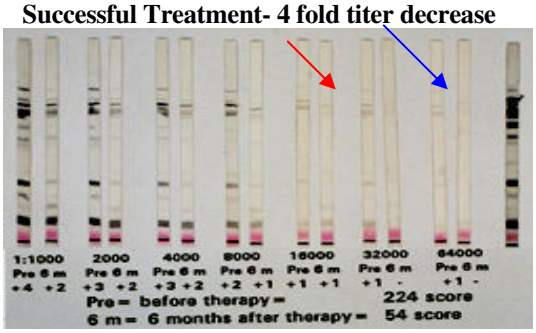
Figure 26 **Western Immunoblot Therapy Titration Tests**

Treatment Failure- No titer decrease



Titration of serum from pre therapy (blue arrow) (1:64,000) 2 yrs, and 2.5 yrs post therapy (red arrow) (1:64,000). No decrease in titer.

Successful Treatment- 4 fold titer decrease



Pre-therapy serum (blue arrow) (1:64,000) at each Dilution is on left while post serum (red arrow) (1:16,000) is on right. 4 fold titer decrease.

Canine *Bartonella* Diseases:

There have been several reports of dogs with diseases caused by a *Bartonella* species.[8,21-24,100-102,136] Five species of *Bartonella* have been found in dogs: *Bartonella henselae, vinsonii, elizabethae, clarridgeiae, and washoensis*. In one case the disease was endocarditis and the *Bartonella* isolated from the valvular lesion was identified as *Bartonella vinsonii* subspecies *berkoffii*. Recently peliosis hepatis occurred in a dog due to *B. henselae* infection.[74] Using the Fe*Bart*® Test, we have tested 746 dogs for *Bartonella* infection and found 155 (21%) infected. The clinical diagnoses for the dogs tested are given below in Table 18.

Table 18 ***Bartonella* in Dogs**

Diagnosis	No. Tested	No. Positive	% Positive
HEALTHY DOGS	**84**	**16***	**19%**
Bartonella-Associated Diseases:			
Gingivitis	**76**	**11**	**14%**
Stomatitis	**11**	**2**	**18%**
Conjunctivitis	**19**	**4**	**21%**
Uveitis	**39**	**8**	**20%**
URI	**20**	**5**	**25%**
Sinusitis & Rhinitis	**12**	**0**	**0%**
Lymphadenopathy	**35**	**10**	**29%**
Fever of Unknown Origin	**41**	**8**	**20%**
Inflammatory Bowel Disease	**15**	**2**	**13%**
Liver Disease	**32**	**7**	**22%**
Arthritis & Polyarthritis	**44**	**16**	**36%**
Diarrhea & Vomiting- Chronic	**17**	**6**	**35%**

CSD Household	5	2**	44%
Heart disease- Murmurs & Endocarditis	35	5	14%
Sub Total:	485	102	21%
No Diagnosis Available	69	14	20%
Other Diseases	192	39	20%
Grand Total:	746	155	21%

* 9 of the 84 healthy infected dogs lived in households with *Bartonella*-infected cats.

** 2 infected dogs lived in a household where a person developed cat scratch disease.

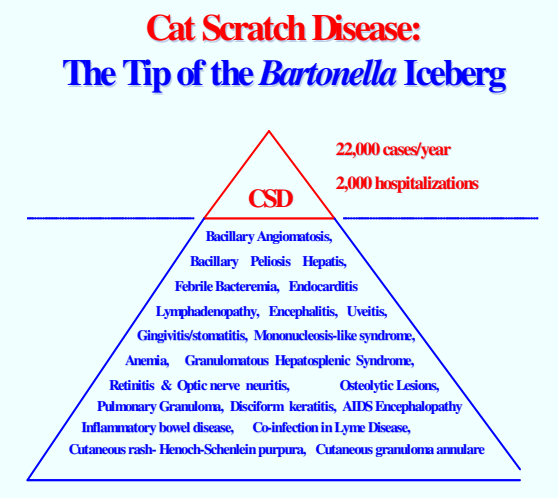
It is interesting to note that, where the diagnosis was indicated, all of the infected dogs had diseases (gingivitis, fevers of unknown origin, lymphadenopathy, uveitis, and endocarditis) that are caused by *Bartonella* in cats and in people. This demonstrates that the pathogenesis of *Bartonella* is similar in various species. Recent serologic surveys have found antibody prevalence to *B. vinsonii* to be 3.6% in North Carolina and Virginia, 9% in US Army dogs and 10% in dogs in Israel.[34] In addition 32% of coyotes in the

western US are antibody positive. Antibody incidence increases in rural areas where tick populations are high. It should be noted that approximately 4% of human cat scratch disease cases are associated only with contact with dogs and not with cats.

Human *Bartonella* Diseases:

There are an increasing number of recognized human *Bartonella* diseases.[2,3,7,21,28,112,125] The best known and "prototype" human *Bartonella* disease is cat scratch disease.[10,96,103] Most of the important human diseases are caused by cat-derived *Bartonella*.[82,89]

It is now known that cat scratch disease is just the "tip of the iceberg" of the diseases caused by *Bartonella* and all *Bartonella* infections are not CSD . For example, concurrent infection with the Lyme disease agent, *Borrelia burgdorferi,* and *Bartonella henselae* was reported in four patients in central New Jersey.[43] All four patients were diagnosed within a 1-month period and evidenced neurological symptoms even after antibiotic therapy for Lyme disease. The finding of coinfection may explain the persistent symptoms seen in some people following even aggressive therapy for Lyme disease (neuroborreliosis). **Human *Bartonella* diseases are probably the most common zoonotic diseases in the US today.**[135] *Bartonella* diseases are often life-threatening in HIV-infected and AIDS patients, transplant recipients, or people on chemotherapy.[18,51,86,105,126,141]



Cat Scratch Disease (CSD): CSD was first recognized in 1889.[103] Although initially clinicians reported that the majority of cases (80%) occur in people under 20 years of age and usually in males, recent studies have shown that the age distribution for CSD cases is half over 21 years of age.[2,4,5,6,10,39,56,72a,104,113,122,125,145] Ninety per cent of patients have some type of cat contact, 57 to 83% have a history of a cat scratch and 4% have a history of dog contact only.[136] There is a definite case seasonality with far more cases occurring in the summer and fall (July to January) that corresponds to the peak flea and arthropod seasons. There are an estimated 22,000 cases of CSD each year in the US, resulting in 2,000 hospitalizations. Many cases of CSD go undiagnosed or misdiagnosed each year because of atypical clinical presentations.[119,122] In more than 90% of the cases, the disease is a benign, self-limiting subacute regional enlargement of lymph nodes (Figure 16). The initial symptoms occur 3-10 days after cat exposure with a small-reddened nodule occurring at the scratch site. These lesions usually persist for several weeks. Later symptoms occur between 12 and 50 days after the cat exposure and consist of enlargement of lymph nodes that drain the scratch site. Low-grade fever and malaise occur in 30% of patients. Less frequent and more severe symptoms may occur and consist of a rash, enlargement of the liver, bone lesions, conjunctivitis and nervous system involvement. The CSD syndrome duration usually lasts between 2 to 4 months and resolves spontaneously. Until recently antibiotics were not shown to be clearly beneficial, but now azithromycin and other antibiotics shorten the course of the disease.[11,12] There is no evidence of communicability of CSD between people. *Bartonella henselae* and *clarridgeiae* have been shown to cause CSD.

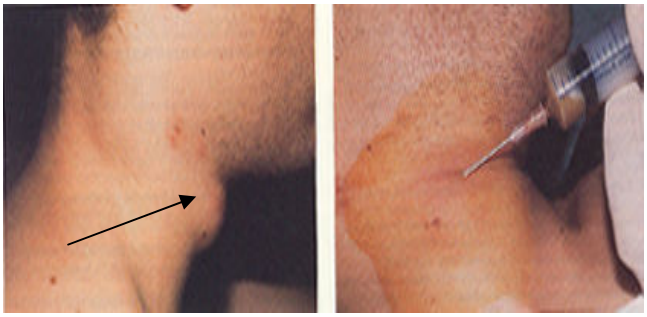


Figure 27
Cat Scratch Disease:
Cervical lymphadenopathy (arrow) in a 17-year-old boy with cat scratch disease who had been scratched by a kitten. Pus was aspirated from the enlarged lymph nodes.
NE J M 340:108, Jan . 14, 1999

Cat Scratch Disease in Children:
Centers for Disease Control and Prevention: Morbidity and Mortality Weekly Report: March 15, 2002, Vol. 51/ No. 10.

Cat-Scratch Disease in Children- Texas, September 2000-August 2001. *S. Kaplan, MD, Texas Children's Hospital, Houston; J. Rawlings, MPH, Texas Dept of Health. C Paddock et al. Div of Viral and Rickettsial Diseases, CDC.* www.cdc.gov/mmwr.[72a]
This CDC report is a one-year study of 32 children with cat scratch disease, median age of 6 years (range: 2-15 years), seen at the Texas Children's Hospital in Houston. All cases were confirmed by serology indicating recent *B. henselae* infection. Fourteen of the 32 children required hospitalization. The study concludes: "The findings emphasize that, although CSD is generally a mild, self-limiting illness, the differential diagnosis often includes more serious conditions (e.g., lymphoma, carcinoma, mycobacterial, fungal infections, neuroblastoma) that might result in protracted hospital stays and lengthy treatments before diagnosis."
Case 1. A 5-year-old boy was hospitalized for a chronic fever reaching 104° F for 12 days and pain in the left upper quadrant for 8 days. Laboratory findings showed a mild leukocytosis and an increased erythrocyte sedimentation rate. Retroperitoneal lymphadenopathy was found by abdominal ultrasound. The boy had been scratched by a kitten 2 months before the onset of illness and had a titer for *B. henselae* of 1:4096 on day 14 of the illness. He recovered completely after antibiotic therapy.
Case 2. A 10-year-old girl with endocarditis and persistent low-grade fever, myalgias and weight loss was hospitalized. An aortic valve homograft was performed. Histology of the vegetative valve lesion showed granulomatous inflammation and numerous

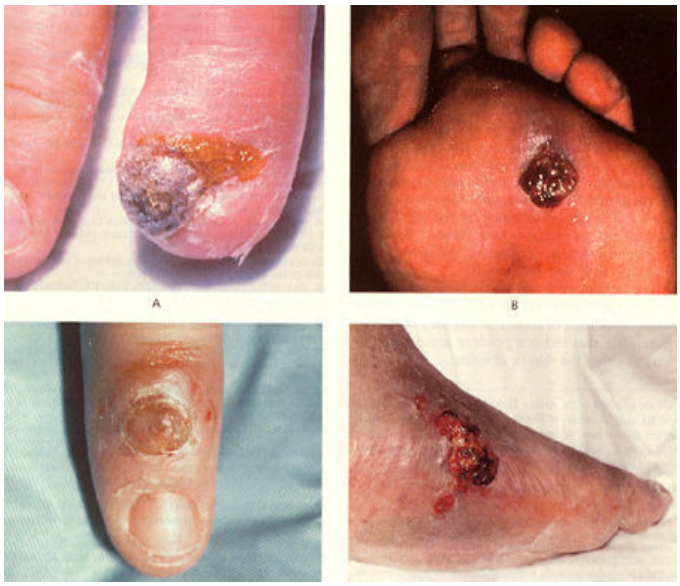
gram-negative bacilli within the vegetations. All cultures of the lesions were sterile. The girl had exposure to birds and kittens and the *B. henselae* titer on day 7 was 1:8192.

Case 3. A 4-year-old boy was hospitalized for intermittent back pain and inability to walk. MRI demonstrated a diffuse abnormal marrow signal in the L1 vertebral body without destruction of the adjacent disc spaces. The boy's back pain resolved without specific therapy within several weeks. There was no history of trauma or cat contact. The *B. henselae* titer was 1:2048 by day 8 of illness.

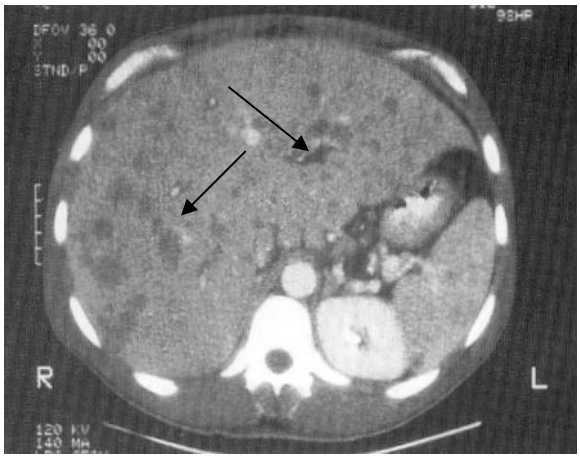
Case 4. A 12-year-old girl was hospitalized after 3 weeks of intermittent fevers (101-105.1° F). There were enlarged and tender inguinal lymph nodes. A colonoscopy showed nodularity with mucosal edema in the terminal ileum. The girl had a recent history of dog and kitten scratches. The *B. henselae* titer during week 4 of illness was 1:8192.

The clinical manifestations of the remaining 28 cases included: fever and regional adenopathy (classic CSD) n=20; chronic fever n=4; Hepatosplenic granuloma n=3 and encephalitis n=1. Fourteen of the 32 children (44%) were hospitalized. Other serious clinical manifestations of *Bartonella henselae* infection in people include: granulomatous conjunctivitis, neuroretinitis, atypical pneumonia, bacillary angiomatosis and peliosis, inflammatory bowel disease and a mononucleosis-like syndrome. This year long study of children with *Bartonella* infection highlights the importance of this zoonosis. Although many *Bartonella* infections are mild or go undiagnosed, some may present with severe clinical signs that require invasive diagnostic techniques. The authors of this study state, "Because Texas Children's Hospital is a referral hospital, the frequency of severe manifestations seen in this series is probably disproportionately high relative to general practice." Although CSD usually causes a more severe syndrome in children, it should be noted that 50% of CSD cases occur in people over 21 years of age. With the advent of accurate serologic assays for the diagnosis of *Bartonella* infection in cats, and with the development of effective and practical antibiotic therapy for infected cats, it appears timely for veterinarians to consider testing all cats, especially kittens, for *Bartonella* infection. This serious public health threat can be greatly reduced by veterinarians with good veterinary medicine and public health awareness.

Figure 28 BA



Bacillary angiomatosis (BA) (Figure 28) is an unusual proliferation of blood vessel tissues that occurs mainly in immunocompromised persons, such as AIDS, cancer therapy, and transplant patients.[2,76,77,78,117,130,134,137,139] However, a few cases involving immunocompetent individuals have recently been reported. Both *Bartonella henselae* and *quintana* have been shown to cause BA. Although every organ system may be affected, BA (top 2 panels) is usually characterized by nodular skin lesions that clinically resemble Kaposi's sarcoma (bottom 2 panels). Enlargement of affected organs, fever, weight loss, and malaise may develop in people with disseminated BA. Both bacteria have been isolated from the blood and affected tissues of patients with BA. Antibiotic therapy is effective in BA. Thus early diagnosis is important in the treatment of BA in HIV-1 infected people.



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NEJM 337:1888, Dec 25, 1997

Figure 29
Bacillary peliosis hepatis (BPH) (left) is the name of a rare, potentially fatal condition affecting mainly the liver of immunocompromised people.[3,105,130,139] It is characterized by blood-filled cysts scattered randomly throughout the liver (arrows). Both *Bartonella henselae* and *quintana* have been shown to cause BPH. Clinical symptoms include fever, weight loss, nausea, diarrhea, abdominal pain, enlargements of organs and lymph nodes. Antibiotic therapy is effective in patients with BPH. Clin. Infect. Dis. 17: 612-624, 1993.

Febrile bacteremia, also known as relapsing bacteremia, is a persistent, relapsing bacteremia caused by either *Bartonella henselae* or *quintana*.[112,115,128,133] The condition is rare and occurs in HIV-infected and in immunocompetent people and may be the modern version of Trench Fever. In immunocompromised people the condition develops slowly, with gradually increasing fatigue, malaise, and weight loss. In immunocompetent people the condition is characterized by a sudden onset of febrile illness that may be accompanied by muscle and joint pain, and headaches. Antibiotic therapy is effective in patients with febrile bacteremia.

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Oroya Fever is caused by *B. bacilliformis* which is transmitted by sand flies that inhabit the high Andes of Peru, Ecuador, and Columbia.[46] Bacteria adhere to the red blood cells in the bloodstream and deform them which leads to anemia. The bacteria also invade endothelial cells and may elicit a proliferation of these cells. The acute phase of Oroya fever may occur in highly fatal epidemics. In the chronic phase of the disease proliferations of small blood vessels in the skin (Verruga peruana) may be mistaken for neoplasms. These lesions are similar to bacillary angiomatosis and Kaposi's sarcoma of AIDS patients that occur in this country.

Trench fever is a non-lethal infection caused by *B. quintana*.[27,42,65,95,133] The disease occurred in epidemic form in Europe during both world wars, and it persists as an unrecognized infection in several parts of the world (middle east) where body louse infestation is common. The bacteria are transmitted by human body lice, which remain infected over a normal lifespan without transovarial transmission. The bacteria are maintained in a human-louse-human cycle, with no known non-human reservoirs. The 14- to 30-day incubation period is followed by a sudden onset of fever, which persists for a few days. About half of the patients have multiple relapses over months to years and organisms may persist in the blood for months even without overt disease. Recently pet cats in this country have been found to be infected with *B. quintana*.[32]

Lymphadenopathy occurs in both humans and animals (cats) infected with various *Bartonella* species.[28,39,76,77,119,139,141,146] The bacteria can localize in and cause enlargement of lymph nodes. In humans the enlarged lymph nodes occur along with other symptoms but may rarely occur as the only indication of infection. Cats infected with *B. henselae* rarely show any signs of infection but some cats have had moderate, painless, lymphadenopathy.

Endocarditis occurs in both humans and animals (dogs) infected with 5 of the *Bartonella* species: *B. henselae, quintana*, *vinsonii*, *elizabethae* and *washoensis*.[21,36,41,67,70,108,109,132,173] The bacteria have surface proteins that cause them to stick to RBCs and endothelial cells which leads to localization in the valves of the heart and to the development of proliferative endocarditis (Figure 30). Three per cent of human endocarditis cases in France are caused by *Bartonella*.[109]

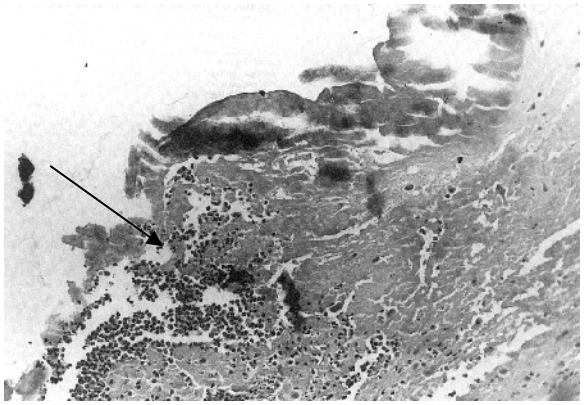

Figure 30 NEJM 345:1321, Nov. 1, 2001

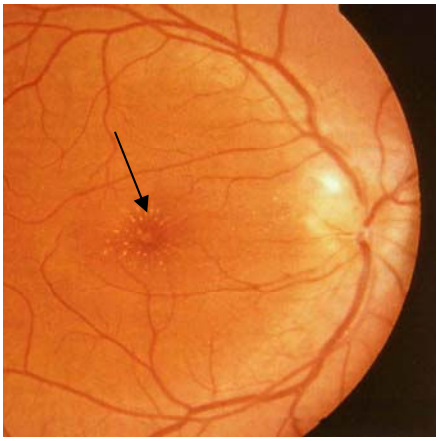

Figure 31
Chorioretinitis caused by *Bartonella henselae*. Bilateral macular papilledema with stellate exudates (arrow) in a boy who lived with a new kitten. NEJM 343: 1459, Nov.16, 2000. There are numerous reports of similar *Bartonella*-induced ocular diseases in cats and

humans (Table5). [73,83,84, Ocular *Bartonella* References]

Concurrent Infection of the Central Nervous System by *Borrelia burgdorferi* and *Bartonella henselae*: Evidence for a Novel Tick-Borne Disease Complex, *E Eskow, MD, R-V Rao, PhD, and E Mordechai, PhD.* Archives of Neurology 58: 1357-1363, September 2001.[43]

This report describes concurrent infection with *Borrelia burgdorferi* and *Bartonella henselae* in four patients in central New Jersey. All four patients were diagnosed within a 1-month period and evidenced neurological symptoms even after antibiotic therapy for Lyme disease. The finding of coinfection may explain the persistent symptoms seen in some people following even aggressive therapy for Lyme disease (neuroborreliosis).

Case 1. A 14-year-old male adolescent developed frontal headaches, fatigue, knee arthralgia, low-grade fever, insomnia, and inability to concentrate in school. Three months earlier he had removed a small tick from his scalp. Further testing revealed antibody to *B. henselae* but not to *B. burgdorferi*. CT brain scans were normal but PCR on a CSF specimen revealed *B. henselae* and *B. burgdorferi* DNA. The patient denied exposure to cats in the months preceding his illness. A live deer tick found in his household was positive for *B. henselae* and *B. burgdorferi* DNA. He recovered fully after a 6-week course of cefotaxime sodium.

Case 2. A 36-year-old man presented with late-stage Lyme disease. Frontal headaches, fatigue, recent memory loss, depression, and arthralgia symptoms persisted despite ceftiaxone sodium therapy. He was serologically positive for *B. henselae* antibodies and *B. henselae* specific DNA was amplified from his blood and a CSF specimen revealed *B. henselae* and *B. burgdorferi* DNA. After additional antimicrobial therapy no *B. henselae* DNA was found in a CFS specimen taken 28 days later and all symptoms resolved.

Case 3. The third patient was a 15-year-old female adolescent who was treated for Lyme disease with doxycycline. Symptoms recurred after therapy over a 3-month period. She had arthralgia, fatigue, headaches, photophobia, depression, insomnia, and inability to concentrate. There was no exposure to cats or known tick bites. She was serologically positive for antibody to *B. henselae* and *B. henselae* and *B. burgdorferi* DNA was found in a CSF specimen. Symptoms did not improve on doxycycline therapy so therapy was changed to azithromycin. Her symptoms promptly resolved on azithromycin therapy, which has been recently shown to be very effective against *Bartonella*.

Case 4. The final case was a 30-year-old woman who became ill 2 weeks after removing 2 small ticks from her skin. She presented with fever, frontal headaches, dizziness, fatigue, and arthralgia in her arms. Several small ticks (*I scapularis*) were removed from her pet cat and were found to be positive for *B. henselae* DNA but were negative for *B. burgdorferi* DNA. The patient was serologically positive for antibodies to *B. henselae* but negative for antibodies to *B. burgdorferi* and negative for DNA of both bacteria in her CSF. Her symptoms resolved during 28 days of oral doxycycline therapy.

Discussion

This is the first report of finding *B. henselae* in deer ticks removed from a pet cat. Ticks are an additional arthropod vector for feline *Bartonella* and may also transmit the bacteria from cats to people and even to dogs. *Bartonella henselae*-induced encephalopathy may be a relatively frequent cause of status epilepticus in school-age children. This pathogen can cause persistent dementia after encephalitis. In addition, neuroophthalmic effects, including blurred vision or loss of vision have been reported. This important paper documents the possible coinfection with *Bartonella henselae,* obtained from cats via ticks that can complicate other tick-borne disease syndromes.[43,45,47,68]

***Bartonella henselae* Induced Mononucleosis-like Syndrome:**

Widening of the Clinical Spectrum of *Bartonella henselae* Infection as Recognized Through Serodiagnostics. *F Massei, et al. Universita di Pisa.* European Journal of Pediatrics 159: 416-419, 2000.

This report describes the clinical features of *Bartonella henselae* infections in 20 Italian children (14 males) within a 12-month period. All were serologically positive for antibodies to *B. henselae*. The mean age was 7 years 4 months with a range from 1 year 1 month to 14 years of age. All children but one had a history of contact with kittens. Clinical manifestations included regional lymphadenopathy in 14 patients, and an infectious mononucleosis-like syndrome in six children. In five patients a severe disorder was first suspected. Fever of unknown origin occurred in 2 children and multiple hepatosplenic granulomatosis occurred in 1 child. Osteolytic lesion of the bone suggested a bone neoplasm in one child whereas a marked inguinal lymphadenopathy suggested Burkett lymphoma in another. This report again demonstrates the severe nature of *Bartonella* infections in some people, especially children. Invasive diagnostic procedures may be required before *Bartonella* infections are considered

ZOONOTIC CASE STUDY:

We have done a detailed study of humans and cats from a household where a case of cat scratch disease had occurred. The cat scratch disease patient was a 27 yr. old married white female with no children. She was scratched on right forearm 4 months before by the hind legs of "Ru", a castrated 5-year-old DSH. "Ru" was a stray obtained from a local shelter. Three cats lived in the household: "Ru","LuLu", "Inky" and no other animals. There was no history of a flea problem. Four months after the

scratch the woman began to gain weight, had fevers, aches, and fatigue. She developed right breast tenderness, amenorrhea, pain in the right axilla and an abscess eventually developed in the right axillary lymph nodes. In addition she developed a lump in her right breast and she was treated with Ampicillin for 2 weeks with only a slight response. Her physician made a tentative diagnosis of a possible breast tumor. However, she was referred to an infectious disease specialist who diagnosed cat scratch disease and treated her with doxycycline for 2 months. The woman made a complete recovery. However, her physician told her to "GET RID OF HER CATS!" She refused and was referred to us for this problem. We tested all 3 of her cats and found them to all be serologically positive and we were able to isolated *B. henselae* from each cat's blood. All 3 cats were treated orally with 100 mg of doxycycline (50 mg BID) for 4 weeks. Post therapy cultures of the 3 cat's bloods were negative for isolation of *B. henselae*.

Feline Blood Donors:

Practicing veterinarians should be aware that *Bartonella* can be transmitted iatrogenically via blood transfusions.[20,57,79,80] We have found that 24 of 67 (36%) of blood donor or potential blood donor cats were infected with *B. henselae* and, in one case, we have transmitted the bacterium via a blood transfusion. Figure 3 shows the seroconversion of the recipient of a blood donation from an infected cat. Specific strong antibody bands against the bacterial proteins developed within 3 to 5 weeks. We were able to isolate bacteria from the blood of the recipient cat and successfully treated the cat with doxycycline. This is an example of iatrogenic spread of a significant public health pathogen that veterinarians must be aware of and be able to prevent. In this regard, all feline blood donors should be tested for *Bartonella* infection before using them as donors.

MORE INFORMATION:

More information is available on our website: www.natvetlab.com

REFERENCES:

1. Abbott RC, Chomel BB, Kasten RW, Floyd-Hawkins KA, Kikuchi Y, Koehler JE, Pedersen NC. Experimental and natural infection with *Bartonella henselae* in domestic cats. Comp Immunol Microbiol Infect Dis. 1997; 20: 41-51. **2.** Adal KA, Cockerell CJ, Petri WA. Cat scratch disease, bacillary angiomatosis, and other infections due to *Rochalimaea*. N Engl J Med, 330: 1509-1515, 1994. **3.** Ashsan, N., M. J. Holman, et al. Peloisis hepatis due to *Bartonella henselae* in transplantation: a hemato-hepato-renal syndrome. Transplantation 1998; 65(7): 1000-3. **4.** Anderson, B., Kelly, C., Threlkel, R. and Edwards, K. Detection of *Rochalimaea henselae* in cat-scratch disease skin test antigens. J Infect Dis, 168: 1034-1036, 1993. **5.** Anderson, B., Lu, E., Jones, D. and Regnery, R. Characterization of a 17-kilodalton antigen of *Bartonella henselae* reactive with sera from patients with cat scratch disease. J Clin Microbiol. 1998; 33: 2358-2365, 1995. **6.** August, J. R. Cat scratch disease. J Am Vet Med Assoc. 1988; 193(3): 312-5. **7.** Ayoub EM, McBride J, Schmiederer M Anderson B. Role of *Bartonella henselae* in the etiology of Henoch-Schonlein purpura. Pediatr Infect Dis J. 2002; 21 (1): 28-31. **8.** Baneth, G., E. B. Breitschwerdt, et al. A survey of tick-borne bacteria and protozoa in naturally exposed dogs from Israel. Vet Parasitol. 1998; 74(2-4): 133-42. **9.** Barka, N. E., Hadfield, T., Patnaik, M., Schwartzman, W. A., Peter JB. EIA for detection of *Rochalimaea henselae* - reactive IgG, IgM, and IgA antibodies in patients with suspected cat-scratch disease. J Infect Dis, 167: 1503-1504, 1993. **10.** Bass, J. W., J. M. Vincent, et al. The expanding spectrum of *Bartonella* infections: II. Cat-scratch disease. Pediatr Infect Dis J. 1997; 16(2): 163-79. **11.** Bass JW, Freitas BC, Freitas AD, *et al.* Prospective randomized double blind placebo-controlled evaluation of azithromycin for treatment of cat-scratch disease. Pediatr Infect Dis J. 1998; 17: 447-52. **12.** Bass, J. W., et. al. Evaluation of antimicrobial treatment of *Bartonella henselae* infections. 1st Int Conference on *Bartonella* as Emerging Pathogens. Tubingen, Germany, March 5-7,1999. Abst. J Microbiol Methods 37: 267-295, 1999. **13.** Batterman, H. J., J. A. Peek, et al. *Bartonella henselae* and *Bartonella quintana* adherence to and entry into cultured human epithelial cells. Infect Immun. 1995; 63(11): 4553-6. **14.** Bergmans, A. M., Groothedde, J-W., Schellekens, J. F. P., van Embden, J. D. A., Ossewaarde, J. M. and Schouls, L. M. Etiology of cat scratch disease: comparison of polymerase chain reaction detection of *Bartonella* (Formerly *Rochalimaea*) and *Afipia felis* DNA with serology and skin tests. J Infect Dis, 171: 916-923, 1995. **15.** Bergmans, A. M., M. F. Peeters, et al. Pitfalls and fallacies of cat scratch disease serology: evaluation of *Bartonella* henselae-based indirect fluorescence assay and enzyme-linked immunoassay. J Clin Microbiol. 1997; 35(8): 1931-7. **16.** Bergmans, A. M., C. M. de Jong, et al. Prevalence of *Bartonella* species in domestic cats in The Netherlands. J Clin Microbiol. 1997; 35(9): 2256-61. **17.** Birtles RJ, Laycock G, Kenny MJ, Shae SE, Day MJ. Prevalence of *Bartonella* species causing bacteraemia in domesticated and companion animals in the United Kingdom. Vet Rec. 2002; 24; 151 (8): 25-229. **18.** Black, J. R., D. A. Herrington, et al. Life-threatening cat-scratch disease in an immunocompromised host. Arch Intern Med. 1986; 146(2): 394-6. **19.** Branley, J., C. Wolfson, et al.. Prevalence of *Bartonella henselae* bacteremia, the causative agent of cat scratch disease, in an Australian cat population. Pathology 1996; 28(3): 262-5. **20**. Breitschwerdt, E. B., and Kordick, D. L. Bartonellosis. J Am Vet Med Assoc, 206: 1928-1931, 1995. **21.** Breitschwerdt, E. B., Kordick, D. L., Malarkey, D. E., Keene, B., Hadfield, T. L. and Wilson, K. Endocarditis in a dog due to infection with a novel *Bartonella* subspecies. J Clin Microbiol, 33: 154-160, 1995. 22. Breitschwerdt, E. B., B. C. Hegarty, et al. Sequential evaluation of dogs naturally infected with *Ehrlichia canis, Ehrlichia chaffeensis, Ehrlichia equi, Ehrlichia ewingii*, or *Bartonella vinsonii*. J Clin Microbiol. 1998; 36 (9): 2645-51. **23.** Breitschwerdt EB, Atkins CE, et al. *Bartonella vinsonii subsp. berkhoffii* and related members of the alpha subdivision of the Proteobacteria in dogs with cardiac arrhythmias, endocarditis, or myocarditis. J Clin Microbiol.1999; 37(11): 3618-26. **24.**

Breitschwerdt EB, Kordick DL. *Bartonella* infection in animals: carriership, reservoir potential, pathogenicity, and zoonotic potential for human infection. Clin Microbiol Rev. 2000; 13: 428-38. **25.** Brogden KA: Polymicrobial diseases of animals and humans. In: Brogden KA, Guthmiller JM, eds. Polymicrobial Diseases. Washington: ASM Press, 2002: 3-20. **26.** Brenner, D. J., O'Connor, S. P., Winkler, H. H. and Steigerwalt, A. G. Proposals to unify the genera *Bartonella* and *Rochalimaea*, with descriptions of *Bartonella quintana* comb. nov., *Bartonella vinsonii* comb. nov., *Bartonella henselae* comb. nov., and *Bartonella elizabethae* comb. nov., and to remove the family *Bartonellaceae* from the order *Rickettsiales*. Int J Syst Bacteriol, 43: 777-786, 1995. **27.** Brouqui P, Houpikian P, Tissot-Dupont H, Raoult, D. Trench fever in homeless patients. Clin Infect Dis, 21: 766, 1995. **28.** Caniza, MA, Granger, DL, Wilson KH, Washington MK, Kordick D, Frush DP, Blitchington RB. *Bartonella henselae*: etiology of pulmonary nodules in a patient with depressed cell-mediated immunity. Clin Infect Dis, 20: 1505-1511, 1995. **29.** Casadevall A, Pirofski L-A. Host-pathogen interactions: redefining basic concepts of virulence and pathogenicity. Infect Immun. 1999; 67: 3703- . **30.** Casadevall A, Pirofski L-A. Host-pathogen interactions: basic concepts of microbial commensalism, colonization, infection, and disease. Infect Immun. 2000; 68 (12): 6511-6518. **31.** CDC. USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus: A summary. MMWR, 44 RR-8: 16, 1995. **32.** Childs, J. E., Rooney, J. A., Cooper, J. L., Olson, J. G. and Regnery, R. L. Epidemiologic observations on infection with *Rochalimaea* species among cats living in Baltimore, Md. J Am Vet Med Assoc, 204: 1775-1778, 1994. **33.** Chomel, B. B., Abbott, R. C., Kasten, R. W., Floyd-Hawkins, K. A., Kass, P. H., Glaser, C. A., Pedersen, N. C. and Koehler, J. E. *Bartonella henselae* prevalence in domestic cats in California: Risk factors and association between bacteremia and antibody titers. J Clin Microbiol., 33: 2445-2450, 1995. **34.** Chomel, B. B., Kasten, R. W., Yamamoto, K., Chang, C., Honadel, T. E., and Kikuchi, Y. Epidemiology of *Bartonella* infections in domestic and wild carnivores and ruminants. 1st

International Conference on *Bartonella* as Emerging Pathogens. Tubingen, Germany, March 5-7,1999. Abstracts. J Microbiol Methods 37: 267-295, 1999. **35.** Clarridge, J. E., Raich, T. J., Pirwani, D., Simon, B., Tsai, L., Rodriguez-Barradas, M. C., Regnery, R., Zollo, A., Jones, D. C., and Rambo, C. Strategy to detect and identify *Bartonella* species in routine clinical laboratory yields *Bartonella henselae* from human immunodeficiency virus-positive patient and unique *Bartonella* strain from his cat. J Clin Microbiol, 33: 2107-2113, 1995. **36.** Daly, J. S., Worthington, M. G., Brenner, D. J., Moss, C. W., Hollis, D.G., Weyant, R. S., Steigerwalt, A. G., Weaver, R. E., Daneshvar, M.I. and O'Connor, S.P. *Rochalimaea elizabethae* sp. nov. isolated from a patient with endocarditis. J Clin Microbiol, 31: 872-881, 1993. **37.** Dehio C. *Bartonella* interactions with endothelial cells and erythrocytes. Trends Microbiol. 2001; 9 (6); 279-85. **38.** Dehio C. Recent progress in understanding *Bartonell*a-induced vascular proliferation. Curr Opin Microbiol. 2003; 6 (1): 61-65. **39.** Dolan, M. J., Wong, M. T., Regnery, R. L., Jorgensen, J. H., Garcia, M., Peters, J. and Drehner, D. Syndrome of *Rochalimaea henselae* adenitis suggesting cat scratch disease. Ann Inter Med, 118: 331-336, 1993. **40.** Droz S, Chi B, Horn E, Steigerwalt AG, Whitney AM, Brenner DJ. *Bartonella koehlerae* sp. nov., isolated from cats. J Clin Microbiol. 1999; 37 (4): 1117-1122. **41.** Drancourt, M., Mainardi, J. L., Brouqui, P., Vandenesch, F., Carta, A., Lehnert, F., Etienne, J., Goldstein, F., Acar, J. and Raoult, D. *Bartonella* (*Rochalimaea*) *quintana* endocarditis in three homeless men. N Engl J Med, 332: 419-423, 1995. **42.** English, C. K., Wear, D. J., Margileth, A. M., Lissner, C. R. and Walsh, G. P. Cat-Scratch Disease isolation and culture of the bacterial agent. JAMA, 259: 1347-1350, 1988. **43.** Eskow E, Rao R-V, Mordechai E. Evidence for a novel tick-borne disease complex,. Arch Neurol. 2001; 58: 1357-1363. **44.** Evans AS. Causation of disease: the Henle-Koch postulates revisited. Yale J. Biol Sci. 1976; 49: 175-195. **45.** Finkelstein JL, Brown TP, O'Reilly KL, Wedincamp J Jr, Foil LD. Studies on the growth of *Bartonella henselae* in the cat flea (Siphonaptera: Pulicidae). J Med Entomol. 2002; 39 (6): 915-919. **46.** Fischer, C. and Kiehn, T. E. *Bartonella* infections. Infect Med, 12: 112, 115-116, 1995. 47. Foil L, Andress E, Freeland RL, Roy AF, Rutledge R, Triche PC, O'Reilly KL. Experimental infection of domestic cats with *Bartonella henselae* by inoculation of *Ctenocephalis felis* (*Siphonaptera: Pulicidae*) feces. J Med Entomol. 1998; 35: 625-628. **48.** Foley JE, et al. Seroprevalence of *Bartonella henselae* in cattery cats: association with cattery hygiene and flea infestation. Vet Q. 1998; 20: 1-5. **49.** Freeland RL, Scholl DT, Rohde KR, Shelton LJ, O'Reilly KL. Identification of *Bartonella*-specific immunodominant antigens recognized by the feline humoral immune system. Clin Diagn Lab Immunol 1999; 6: 558-66. **50.** uhrmann O, Arvand M, Gohler A, Schmid M, Krull M, Hippenstiel S, Dehio C, Suttorp N. *Bartonella henselae* induces NF-kappB-dependent upregulation of adhesion molecules in cultured human endothelial cells: possible role of outer membrane proteins as pathogenic factors. Infect Immun. 2001; 69 (8): 5088-97. **51.** Grant S, Olsen CW. Preventing zoonotic diseases in immunocompromised persons: The role of physicians and veterinarians. Emerg Infect Dis. 1999; 5 (1): 159-163. **52.** Greene CE, McDermott M, Jameson PH, Atkins CL, Marks AM. *Bartonella henselae* infection in cats: evaluation during primary infection, treatment, and rechallenge infection. J Clin Microbiol 1996;34: 1682-5. **53.** Groves, M. G. and Harrington, K. S. *Rochalimaea henselae* infections: Newly recognized zoonoses transmitted by domestic cats. J Am Vet Med Assoc, 1994; 204: 267-271. **54.** Guptill L, Slater L, Wu CC, Glickman LT, Lin TL, Welch DF, Crippen JT, HogenEsch H. Immune response of neonatal specific pathogen-free cats to experimental infection with *Bartonella henselae*. Vet Immunol Immunopathol. 1999; 71 (3-4): 233-243. **55.** Guptill L, Slater L, Wu CC, Lin TL, Glickman LT, Welch DF. Experimental infection of young specific pathogen-free cats with *Bartonella henselae*. J Infect Dis. 1997; 176 (1): 206-16. **56.** Guptill L, Slater L, Wu CC, Lin TL, Glickman LT, Welch DF, Tobolski J, HogenEsch H. Evidence of reproductive failure and lack of perinatal transmission of *Bartonella henselae* in experimentally infected cats. Vet

Immunol Immunopathol. 1998; 65: 177-89. **56a**. Gurfield AN, Boulouis H-J, Chomel BB, Heller R, Kasten RW, Yamamoto K, Piemont Y. Coinfection with *Bartonella clarridgeiae* and *Bartonella henselae* and with different *Bartonella henselae* strains in domestic cats. J Clin Microbiol 35:2120-2123, 1997. **56b.** Hamilton, D. H., Zangwill, K. M., Hadler, J. L. and Cartter, M. L. Cat- scratch disease-Connecticut, 1992-1993. J Infect Dis, 172: 570-573, 1995. **57.** Hardy, W.D., Jr., Zuckerman, E.E., Baron, P., Gold, J.W.M., Keihn, T., Polsky, P. and Armstrong, D. Immunogenic proteins of *Bartonella henselae* defined by western immunoblots with naturally infected cat sera. 95th General Meeting, American Society for Microbiology, Washington, D. C. May 21-25, 1995. **58.** Hardy WD Jr, Zuckerman EE, Corbishley J. *et al*. Successful therapy of *Bartonella henselae* bacteremic healthy pet cats. Annual Meeting, 1nfectious Disease Society of America, New Orleans, September, 1996. **59.** Hardy WD Jr, Zuckerman EE, Gold JWM, *et al. Bartonella henselae*, cats and HIV-1 infection. 1997 Annual Meeting of the Institute of Human Virology, Baltimore, MD, September 15-21, 1997, Abstract 168. **60.** Hardy WD Jr, Zuckerman EE, Corbishley J. Seroprevalence of *Bartonella*-infection in healthy and diseased cats in the United States and Caribbean: Evidence for *Bartonella*-induced diseases in cats. International Conference of the American Society for Rickettsiology, Big Sky, Montana, August 17-22, 2001. **61.** Hardy WD Jr, Zuckerman EE, Corbishley J. *et al*. Efficacy of high dose, long duration Doxycycline or Azithromycin treatment for *Bartonella* infections in pet cats. International Conference of the American Society for Rickettsiology, Big Sky, Montana, August 17-22, 2001. **62.** Hardy WD J., Zuckerman EE, Corbishley J. Serological evidence that *Bartonella* cause gingivitis and stomatitis in cats. American Veterinary Dental Society Meeting, Savannah, GA, October 2002. **63.** Hardy WD Jr, Corbishley J, Zuckerman EE. Azithromycin therapy of *Bartonella*-infected cats with gingivitis and stomatitis. American Veterinary Dental Society Meeting, Savannah, GA, October 2002. **64.** Heller R, Artois M, Xemar V, De Briel D, Gehin H, Jaulhac B, Monteil H, Piemont Y. Prevalence of *Bartonella. henselae* and *Bartonella clarridgeiae* in stray cats. J Clin Microbiol. 1997; 35: 1327-1331. **65.** Herrmann, JE, Hollingdale MR, Collins MF, Vinson W. Enzyme immunoassay and radioimmunoprecipitation tests for the detection of antibodies to *Rochalimaea* (*Rickettsia) quintana* (39655). Soc Exp Biol Med, 154: 285-288, 1977. **66.** Hoppenstiel S, Suttorp

N. Interaction of pathogens with the endothelium. Thromb Haemost. 2003; 89 (1): 18-24. **67.** Holmes, AH, Greenough TC, Balady GL, Regnery R., Anderson BE, O'Keane JC, Fonger JD, McCrone EL. *Bartonella henselae* endocarditis in an immunocompetent adult. Clin Infect Dis, 21: 1004-1007, 1995. **68.** Ishida C, Tsuneoka H, Iino H, Murakami K, Inokuma H, Ohnishi T, Tsukahara M. *Bartonella henselae* infection in domestic cat and dog fleas. Kansenshogaku Zasshi. 2001; 75 (2): 133-6. **69.** Jacomo V, Kelly PJ, Raoult D. Natural history of *Bartonella* infections (an exception to Koch's postulate). Clin Diagn Lab Immunol. 2002; 9 (1): 8-18. **70.** Jalava, J., Kotilainen, P., Nikkari, S., Skurnik, M., Vanttinen, E., Lehtonen, O-P., Eerola, E. and Toivanen, P. Use of the polymerase chain reaction and DNA sequencing for detection of *Bartonella quintana* in the aortic valve of a patient with culture-negative infective endocarditis. Clin Infect Dis, 21: 891-896, 1995. **71.** Jameson, P., Greene, C., Regnery, R., Dryden, M., Marks, A., Brown, J., Cooper, J., Glaus, B., Greene, R. Prevalence of *Bartonella henselae* antibodies in pet cats throughout regions of north America. J Infect Dis, 172: 1145-1149, 1995. **72.** Joblet, C., Roux, V., Drancourt, M., Gouvernet, J. and Raoult, D. Identification of *Bartonella* (*Rochalimaea*) species among fastidious gram-negative bacteria on the basis of the partial sequence of the citrate-synthase gene. J Clin Microbiol, 33: 1879-1883, 1995. **72a.** Kaplan S, Paddock C, *et al*. Cat-Scratch Disease in Children- Texas, September 2000-August 2001. Centers for Disease Control and Prevention: Morbidity and Mortality Weekly Report: March 15, 2002, 51: (10). **73.** Ketring KL, Zuckerman EE, Hardy WD Jr. *Bartonella*: a new etiological agent of feline ocular diseases. J Amer Animal Hosp Assoc. 40: 6-12, 2004. **74.** Kitchell B. E., Fan, T. M., Kordick, D., Breitschwerdt, E. B., Wollenberg, G., and Lichtensteiger, C. A. Peliosis hepatis in a dog infected with *Bartonella henselae*. J Am Vet med Assoc, 216: 519-523, 2000. **75.** Koehler, J. E., Glaser, C. A. and Tappero, J. W. *Rochalimaea henselae* infection A new zoonosis with the domestic cat as reservoir. JAMA, 271: 531-535, 1994. **76.** Koehler, J. E., LeBoit, P. E., Egbert, B. M. and Berger, T. G. Cutaneous vascular lesions and disseminated cat-scratch disease in patients with the acquired immunodeficiency syndrome (AIDS) and AIDS-related complex. Ann Intern Med, 109: 449-455, 1988. **77.** Koehler, J. E., Quinn, F. D., Berger, T. G., LeBoit, P. E. and Tappero, J. W. Isolation of *Rochalimaea* species from cutaneous and osseous lesions of bacillary angiomatosis. N Engl J Med. 327: 1625-1631, 1992. **78.** Koehler, J. E. and Tappero, J. W. Bacillary angiomatosis and bacillary peliosis in patients infected with human immunodeficiency virus. Clin Infect Dis, 17: 612-24, 1993. **79.** Kordick, D. L. and Breitschwerdt, E. B. Intraerythrocytic presence of *Bartonella henselae*. J Clin Microbiol, 33: 1655-1656, 1995. **80.** Kordick DL, Breitschwerdt EB. Relapsing bacteremia after blood transmission of *Bartonella* henselae to cats. Am J Vet Res 1997; 58: 492-7. **81.** Kordick DL, Brown TT, Shin KO, et al.: Clinical and pathologic evaluation of chronic *Bartonella henselae* or *Bartonella clarridgeiae* infection in cats. J Clin Microbiol 37:1536-1547, 1999. **82.** Krauss H, Weber A, Appel M, Enders B, Isenberg HD, Schiefer HG, Slenczka W, von Graevenitz A, Zahner H. 2003. Bacterial Zoonoses. p 173-252. *In* Zoonoses: Infectious Diseases Transmissible from Animal to Humans. ASM press, Washington, DC. **83.** Lappin MR, Black JC. *Bartonella spp* infection as a possible cause of uveitis in a cat. J Am Vet Med Assoc 1999; 214:1205-1207. **84.** Lappin MR, Kordick DL, Breitschwerdt EB. *Bartonella spp* antibodies and DNA in aqueous humour of cats. J Feline Med Surg. 2000;2(1):61-8. 85. Larson, A. M., Dougherty, M. J., Nowowiejski, D. J., Welch, D. F., Matar, G. M., Swaminathan, B. and Coyle, M. B. Detection of *Bartonella* (*Rochalimaea*) *quintana* by routine acridine orange staining of broth blood cultures. J Clin Microbiol, 32: 1492-1496, 1994. **86.** Lucey, D., Dolan, M. J., Moss, C. W., Garcia, M.,

Hollis, D. G., Wegner, S., Morgan, G. and Almeida, R., Leong, D., Greisen, K.S., Welch, D.F., and Slater, L.N. Relapsing illness due to *Rochalimaea henselae* in immunocompetent hosts: Implication for therapy and new epidemiological associations. Clin Infect Dis, 14: 683-8, 1992. **87.** Maeno N, Oda H, Yoshiie K, Wahid MR, Fujimura T, Matayoshi S. Live *Bartonella henselae* enhances endothelial cell proliferation without direct contact. Microb Pathog. 1999; 27 (6): 419-27. **88.** Maeno N, Yoshiie K, Matayoshi S, Fujimura T, Mao S, Wahid MR, Oda H. A heat-stable component of *Bartonella henselae* upregulates intercellular adhesion molecule-1 expression on vascular endothelial cells. Scand J Immunol. 2002; 55 (4): 366-72. **89.** Margileth AM, Hayden GF. Cat scratch disease:From feline affection to human infection. N Engl J Med, 329:53-54, 1993. **90.** Marullo, S., Jaccard, A., Roulot, D., Mainguene, C. and Clauvel, J. P. Identification of the *Rochalimaea henselae* 16S rRNA sequence in the liver of a french patient with bacillary peliosis hepatis. J Infect Dis, 166: 1462, 1992. **91.** Maurin, M., Roux, V., Stein, A., Ferrier, F., Viraben, R. and Raoult, D. Isolation and characterization by immunofluorescence, sodium dodecyl sulfate- polyacrylamide gel electrophoresis, western blot, restriction fragment length polymorphism-PCR, 16S rRNA gene sequencing, and pulse-field gel electrophoresis of *Rochalimaea quintana* from a patient with bacillary angiomatosis. J Clin Microbiol, 32: 1166-1171, 1994. **92.** McDermott W. Microbial persistence. Yale J Biol Med. 1958; 30: 257-291. **93.** Mehock, JR, Greene CE, Gherardini FC, Hahn T-W, Krause DC. *Bartonella henselae* invasion of feline erythrocytes in vitro. Infect Immunol. 1998; 66 (7): 3462-3466. **94.** Mikolajczyk MG, O'Reilly KL. Clinical disease in kittens inoculated with a pathogenic strain of *Bartonella henselae*. Am J Vet Res. 2000: 61: 375-379. **95.** Myers, W. F., Grossman, D. M. and Wisseman, C. L., Jr Antibiotic susceptibility patterns in *Rochalimaea quintana*, the agent of Trench Fever. Antimicrob Agents Chemother, 25: 690-693, 1984. **96.** Noah, D. L., J. S. Bresee, et al. Cluster of five children with acute encephalopathy associated with cat-scratch disease in south Florida. Pediatr Infect Dis J. 1995; 14(10): 866-9. **97.** Noah DL, et al.: Survey of veterinary professionals and other veterinary conference attendees for antibodies to *Bartonella henselae* and *B. quintanna*. J Am Vet Med Assoc. 1997; 210: 342-344. **98.** Norman, A. F., Regnery, R., Greene, C. and Krause, D. C. Differentiation of *Bartonella*-like isolates at the species level by PCR-restriction fragment length polymorphism in the citrate synthase gene. J Clin Microbiol, 33: 1797-1803, 1995. **99.** O'Reilly KL, Bauer RW, Freeland RL Foil LD, Hughes KJ, Rohde KR, Roy AF, Stout RW, Triche PC. Acute clinical disease in cats following infection with a pathogenic
strain of *Bartonella henselae* (LSU16). Infect Immun. 1999; 67 (6): 3066-3072. **100.** Pappalardo, B. L., M. T. Correa, et al.

Epidemiologic evaluation of the risk factors associated with exposure and seroreactivity to *Bartonella* vinsonii in dogs. Am J Vet Res. 1997; 58(5): 467-71. **101.** Pappalardo BL, Brown T, *et al*. Granulomatous disease associated with *Bartonella* infection in 2 dogs. J Vet Intern Med. 2000; 14 (1): 37-42. **102.** Pappalardo BL, Brown TT, Tompkins M, Breitschwerdt EB. Immunopathology of *Bartonella vinsonii* (*berkhoffii*) in experimentally infected dogs. Vet immunol Immunopathol. 2001; 83 (3-4): 125-147. **103.** Parinaud H. Conjonctivite infectieuse transmise par les animaux. Ann Ocul 1889; 101: 252-253. **104.** Perkins, B. A., Swaminathan, B., Jackson, L. A., Brenner, D. J., Wenger, J. D. and Regnery, R. L. Case 22-1922 - Pathogenesis of cat scratch disease. N Engl J Med, 327: 1599-1600, 1992. **105.** Perkocha, L. A., Geaghan, S. M., Yen, T. S. B., Nishimura, S. L., Chan, S. P., Garcia-Kennedy, R., Honda, G., Stoloff, A. C., Klein, H.Z., Goldman, R.L., Van Meter, S., Ferrell, L.D, LeBoit, P.E. Clinical and pathological features of bacillary peliosis hepatis in association with human immunodeficiency virus infection. N Engl J Med, 323: 1581-1586, 1990. **106.** Pickett DA, Welch DF, Susceptibility testing of *Bartonella species*. ASM Meeting Abstr. Washington, DC, May, 1995. **107.** Pretorius AM, Kelly PJ, Birtles RJ, Raoult D. Isolation of *Bartonella henselae* from a serologically negative cat in Boemfontein, South Africa. J S Afr Vet Assoc. 1999; 70 (4): 154-155. **108.** Roux, V., Eykyn, S. J., Wyllie, S. and Raoult, D. *Bartonella vinsonii subsp. berkhoffi* as an agent of afebrile blood culture-negative endocarditis in a human. J Clin Microbiol, 38: 1698-1700, 2000. **109.** Raoult, D., Fournier, R. J., Drancourt, M., Marrie, T. J., et. al. Diagnosis of 22 new cases of *Bartonella* endocarditis. Ann Intern Med, 125: 646-652, 1996. **110.** Reed, J. A., Brigati, D. J., Flynn, S. D., McNutt, N. S., Min, K. W.,Welch, D. F. and Slater, L. N. Immunocytochemical identification of *Rochalimaea henselae* in bacillary (epithelioid) angiomatosis, parenchymal bacillary peliosis, and persistent fever with bacteremia. Amer J Surg Pathol, 16: 650-657, 1992. **111.** Regnery, R., Martin, M. and Olson, J. Naturally occurring "*Rochalimaea henselae*" infection in domestic cat. Lancet, 340: 557, 1992. **112.** Regnery, R. L., Anderson, B. E., Clarridge, J. E., Rodriguez-Barradas, M. C., Jones, D. C. and Carr, J. H. Characterization of an novel *Rochalimaea* species, *R. henselae* sp. nov., Isolated from blood of a febrile, human immunodeficiency virus-positive patient. J Clin Microbiol, 30: 265-273, 1992. **113.** Regnery, R. L., Olson, J. G., Perkins, B. A. and Bibb, W. Serological response to "*Rochalimaea henselae*" antigen in suspected cat-scratch disease. Lancet, 339: 1443, 1992. **114.** Regnery, R. and Tappero, J. Unraveling mysteries associated with cat- scratch disease, bacillary angiomatosis, and related syndromes. Emerg Infect Dis, 1: 16-21, 1995. **115.** Regnery, R. L., Childs, J. E. and Koehler, J. E. Infections associated with *Bartonella* species in persons infected with human immunodeficiency virus. Clin Infect Dis, 21(Sup): S94-S98, 1995. **116.** Regnery RL, Rooney JA, Johnson AM, *et al.* Experimentally induced *Bartonella henselae* infections followed by challenge exposure and antimicrobial therapy in cats. Am J Vet Res 1996; 57: 1714-9. Erratum in: Am J Vet Res 1997;58:803. **117.** Relman, D. A., Loutit, J. S., Schmidt, T. M., Falkow, S. and Tompkins, L. S. The agent of bacillary angiomatosis: An approach to the identification of uncultured pathogens. N Engl J Med, 323: 1573-1580, 1990. **118.** Resto-Ruiz SI, Schmiederer M, Sweger D, Newton C, Klein TW, Friedman H, Anderson BE. Induction of a potential paracrine angiogenic loop between human THP-1 macrophages and human microvascular endothelial

cells during *Bartonella henselae* infection. Infect Immun. 2002; 70 (8): 4564-70. **119.** Ridder GJ, Sander A, Richter B. Clinical manifestations of cat-scratch disease in the head and neck. 1st Intn Conf on *Bartonella* as Emerging Pathogens. Tubingen, Germany, March 5-7,1999. Abst. J Microbiol Methods 37: 267-295, 1999. **120.** Rodriguez-Barradas, M. C., Hamill, R. J., Houston, E. D., Georghiou, P. R., Clarridge, J. E., Regnery, R. L. and Koehler, J. E. Genomic fingerprinting of *Bartonella* species by repetitive element PCR for distinguishing species and isolates. J Clin Microbiol, 33: 1089-1093, 1995. **121.** Roux, V. and Raoult, D. Inter- and Intraspecies identification of *Bartonella* (*Rochalimaea*) species. J Clin Microbiol, 33: 1573-1579, 1995. **122.** Sander A, Ridder GJ. Cat-scratch disease- not only a children's disease. 1st International Conference on *Bartonella* as Emerging Pathogens. Tubingen, Germany, March 5-7,1999. Abstracts. J Microbiol Methods 37: 267-295, 1999. 123. Sander A, Posselt M, Bohm N, Ruess M, Altwegg M. Detection of *Bartonella henselae* DNA by two different PCR assays and determination of the genotypes of strains involved in histologically defined cat scratch diseases. J Clin Microbiol. 1999; 37 (4): 993-997. **124.** Schulein R, Dehio C. The VirB/VirD4 type IV secretion system of *Bartonella* is essential for establishing intraerythrocytic infection. Mol Microbiol. 2002; 46 (4): 1053-1067. **125.** Schwartzman, W. A. Infections due to *Rochalimaea*: The expanding clinical spectrum. Clin Infect Dis, 15: 893, 1992. **126.** Schwartzman, W. A., Patnaik, M., Angulo, F. J., Visscher, B. R., Miller, E. N. and Peter, J. B. *Bartonella* (*Rochalimaea*) antibodies, dementia, and cat ownership among men infected with human immunodeficiency virus. Clin Infect Dis, 21: 954-959, 1995. **127.** Shaw SE, Birtles RJ, Day MJ. Arthropod-transmitted infectious diseases of cats. J Feline Med & Surg. 201; 3: 193-209. **128.** Slater, L. N., Welch, D. F., Hensel, D. and Coody, D. W. A newly recognized fastidious gram-negative pathogen as a cause of fever and bacteremia. N Engl J Med, 323: 1587-1592, 1990. **129.** Slater, L. N., Coody, D. W., Woolridge, L. K. and Welch, D. F. Murine antibody responses distinguish *Rochalimaea henselae* from Rochalimaea quintana. J Clin Microbiol, 30: 1722-1727, 1992. **130.** Slater, L. N., Welch, D. F. and Min, K. W. *Rochalimaea henselae* causes bacillary angiomatosis and peliosis hepatis. Arch Intern Med, 152: 602-606, 1992. **131.** Song, J-H., Lee, C., Chang, W. H., Choi, S. W., Choi, J. E., Kim, S. Y., Cho, S. R. and Ryu, J., Pai, C.H. Short-course Doxycycline treatment versus conventional tetracycline therapy for Scrub Typhus: A multicenter randomized trial. Clin Infect Dis, 21: 506-510, 1995. **132.** Spach, D. H., Kanter, A. S., Daniels, N. A., Nowowiejski, D. J., Larson, A. M., Schmidt, R. A., Swaminathan, B. and Brenner, D. J. *Bartonella* (*Rochalimaea*) species as a cause of apparent "culture-negative" endocarditis. Clin Infect Dis, 20: 1044-1047, 1995. **133.** Spach, DH, Kanter AS, Dougherty MJ, Larson AM, Coyle MB, Brenner DJ, Swaminathan B, Matar GM, Welch DF, Root RK, Stamm, WE. *Bartonella* (*Rochalimaea*) quintana bacteremia in inner-city patients with chronic alcoholism. N Engl J Med, 332: 424-428, 1995. **134.** Tompkins, D. C. and Steigbigel, R. T. *Rochalimaea's* role in cat scratch disease and bacillary angiomatosis. Ann Intern Med, 118: 388-390, 1993. **135.** Tompkins,

L. S. *Rochalimaea* infections are they zoonoses?. JAMA, 271: 553-554, 1994. **136.** Tsukahara, M, Tsuneoka H, Iino H, Ohno K, Murano I. *Bartonella henselae* infection from a dog. Lancet 1998; 352: 1682. **137.** Welch, D. F., D. A. Pickett, et al. Rochalimaea henselae sp. nov., a cause of septicemia, bacillary angiomatosis, and parenchymal bacillary peliosis. J Clin Microbiol. 1992; 30(2): 275-80. **138.** Welch DF, Hensel DM, Pickett DA, San Joaquin VH, Robinson A, Slater LN. Bacteremia due to *Rochalimaea henselae* in a child: practical identification of isolates in the clinical laboratory. J Clin Microbiol, 31: 2381, 1993. **139.** Welch, D. F., Pickett, D. A., Slater, L. N., Steigerwalt, A. G. and Brenner, D. J. *Rochalimaea henselae* sp. nov., a cause of septicemia, bacillary angiomatosis, and parenchymal bacillary peliosis. J Clin Microbiol, 30: 275-280, 1992. **140.** Wise JK Heathcott BL, Gonzalez ML. Results of the AVMA survey on companion animal ownership in US pet-owning households. J Am Vet Med Assoc. 221; 11: 1572-73. **141.** Wong, M. T., Dolan, M. J., Lattuada, C. P., Jr, Regnery, R. L., Garcia, M. L., Mokulis, E. C., LaBarre, R. C., Ascher, D. P. Delmar, J.A., Kelly, J.W., Leigh, D. R., McRae, A.C., Reed, J.B., Smith, R.E. and Melcher, G.P. . Neuroretinitis, aseptic meningitis, and lymphadenitis associated with *Bartonella* (*Rochalimaea*) *henselae* infection in immunocompetent patients and patients infected with human immunodeficiency virus type 1. Clin Infect Dis, 21: 352-360, 1995. **142.** Wong MT, Thornton DC, Kennedy RC, Dolan MJ. A chemically defined liquid medium that supports primary isolation of *Rochalimaea* (*Bartonella*) *henselae* from blood and tissue specimens. J Clin Microbiol, 1995; 33: 742-744. **142a.** Xu YH, Lu ZY, Ihler, GM. Purification of deformin, an extracellular protein synthesized by *Bartonella bacilliformis* which causes deformation of erythrocyte membranes. Biochim. Biophys. Acta. 1995; 1234: 173-83. **143.** Yamamoto K, Chomel BB, Kasten RW, Hew CM, Weber DK, Lee WI. Experimental infection of specific pathogen free (SPF) cats with two different strains of *Bartonella henselae* type I: a comparative study. Vet Res. 2002; 33 (6): 669-684. **144.** Yamamoto K, Chomel BB, Kasten RW, Hew CM, Weber DK, Lee WI, Koehler JE, Pedersen NC. Infection and re-infection of domestic cats with various *Bartonella* species or types: *B. henselae* type I is protective against heterologous challenge with *B. henselae* type II. Vet Microbiol. 2003; 92 (1-2): 73-86. **145.** Zangwill, K. M., Hamilton, D. H., Perkins, B. A., Regnery, R. L., Plikaytis, B. D., Hadler, J. L., Cartter, M. L, Wenger, J. CSD in Connecticut: Epidemiology, risk factors, and evaluation of a new diagnostic test. N Engl J Med, 329: 8, 1993. **146.** Zimmermann R, Kempf VA, Schiltz E, Oberle K, Sander A. Hemin binding, functional expression, and complementation analysis of pap 31 from *Bartonella henselae*. J. Bacteriol. 2003; 185 (5): 1739-1744.

Bartonella-Ocular Diseases References:

1. Boito A. Oculo-glandular localization of benign lymphoreticulosis by inoculation (cat-scratch disease). Description of a case Minerva Pediatr 1965; 17: 1551-5. **2.** Sweeney VP, Drance SM. Optic neuritis and compressive neuropathy associated with cat scratch disease. Can Med Assoc J 1970; 103: 1380-1. **3.** Moriarty RA, Margileth AM. Cat scratch disease. Infect Dis Clin North Am. 1987;1:575-90. **4.** Le HH, Palay DA, Anderson B, Steinberg JP. Conjunctival swab to diagnose ocular cat scratch disease. Am J Ophthalmol. 1994; 118: 249-50. **5.** McCrary B, Cockerham W, Pierce P. Neuroretinitis in cat-scratch disease associated with the macular star. Pediatr Infect Dis J. 1994;13: 838-9. **6.** Hunt L. Ocular cat scratch disease. Insight. 1995; 20: 28-9. **7.** Kruse LP, Engbaek K. Perinaud's oculoglandular syndrome as a manifestation of cat-scratch disease. Ugeskr Laeger. 1995; 157: 4137-8. **8.** Zacchei AC, Newman NJ, Sternberg P. Serous retinal detachment of the macula associated with cat scratch disease. Am J Ophthalmol. 1995; 120:796-7. **9.** Madu AA, Mayers M. Ocular manifestation of systemic infections. Curr Opin Ophthalmol. 1995; 6: 88-91. **10.** Wong MT, Dolan MJ, Lattuada CP Jr, *et al*. Neuroretinitis, aseptic meningitis, and lymphadenitis associated with *Bartonella* (Rochalimaea) henselae infection in immunocompetent patients and patients infected with human immunodeficiency virus type 1. Clin Infect Dis. 1995; 21: 352-60. **11.** Maxwell SM. Sudden onset of blurred vision in a thirteen-year-old girl. Pediatr Infect Dis J. 1995; 14: 1016-19. **12.** Yamashita CA, Mielle A, Renko NS, *et al*. Parinaud syndrome caused by *Bartonella* henselae: case report. Rev Inst Med Trop Sao Paulo. 1996; 38: 437-40. **13.** Madu AA, Mayers M. Ocular manifestation of systemic infections. Curr Opin Ophthalmol. 1996; 7: 85-90. **14.** Soheilian M, Markomichelakis N, Foster CS. Intermediate uveitis and retinal vasculitis as manifestations of cat scratch disease.Am J Ophthalmol. 1996; 122: 582-4. **15.** Huang MC, Dreyer E. Parinaud's oculoglandular conjunctivitis and cat-scratch disease. Int Ophthalmol Clin. 1996; 36: 29-36. **16.** Newsom RW, Martin TJ, Wasilauskas B. Cat-scratch disease diagnosed serologically using an enzyme immunoassay in a patient with neuroretinitis. Arch Ophthalmol. 1996; 114: 493-4. **17.** Soheilian M, Markomichelakis N, Foster CS. Intermediate uveitis and retinal vasculitis as manifestations of cat scratch disease. Am J Ophthalmol. 1996; 122: 582-4. **18.** McGrath N, Wallis W, Ellis-Pegler R, Morris AJ, Taylor W. Neuroretinitis and encephalopathy due to *Bartonella* henselae infection. Aust N Z J Med. 1997; 27: 454. **19.** Cunningham ET Jr, McDonald HR, Schatz H, Johnson RN, Ai E, Grand MG. Inflammatory mass of the optic nerve head associated with systemic *Bartonella* henselae infection. Arch Ophthalmol. 1997; 115: 1596-7. **20.** Rothova A, Kerkhoff F, Hooft HJ, Ossewaarde JM. *Bartonella* serology for patients with intraocular inflammatory disease. Retina. 1998; 18: 348-55. Erratum in: Retina 1999;19(3):260. **21.** Ormerod LD, Skolnick KA, Menosky MM, Pavan PR, Pon DM. Retinal and choroidal manifestations of cat-scratch disease. Ophthalmology.1998; 105: 1024-31. **22.** Reed JB, Scales DK, Wong MT, Lattuada CP Jr, Dolan MJ, Schwab IR. *Bartonella* henselae neuroretinitis in cat scratch disease. Diagnosis, management, and sequelae. Ophthalmology. 1998; 105: 459-66. **23.** Gaebler JW, Burgett RA, Caldemeyer KS. Subacute orbital abscess in a four-year-old girl with a new kitten. Pediatr Infect Dis J. 1998; 17: 844-6. **24.** Pollock SC, Kristinsson J. Cat-scratch disease manifesting as unifocal helioid choroiditis.Arch Ophth.1998; 116: 1249-51. **25.** ur Rehman S, Metcalfe TW, Barnham M. Anterior uveitis associated with cat scratch disease. Br J Ophth. 1998; 82:587-8.

26

26. Warren K, Goldstein E, Hung VS, Koehler JE, Richardson W. Use of retinal biopsy to diagnose *Bartonella* (formerly Rochalimaea) henselae retinitis in an HIV-infected patient. Arch Ophthalmol. 1998; 116: 937-40. **27.** Ormerod LD, Dailey JP. Ocular manifestations of cat-scratch disease. Curr Opin Ophthalmol. 1999; 10: 209-16. **28.** Lombardo J. Cat-scratch neuroretinitis. J Am Optom Assoc. 1999; 70: 525-30. **29.** Grando D, Sullivan LJ, Flexman JP, Watson MW, Andrew JH. *Bartonella* henselae associated with Parinaud's oculoglandular syndrome. Clin Infect Dis. 1999; 28:1156-8. **30.** Solley WA, Martin DF, Newman NJ, King R, Callanan DG, Zacchei T, Wallace RT, Parks DJ, Bridges W, Sternberg P Jr. Cat scratch disease: posterior segment manifestations. Ophthalmology. 1999; 106: 1546-53. **31.** Kerkhoff FT, Ossewaarde JM, de Loos WS, Rothova A. Presumed ocular Bartonellosis. Br J Ophthalmol.1999; 83: 270-5. **32.** Gray AV, Reed JB, Wendel RT, Morse LS. *Bartonella* henselae infection associated with peripapillary angioma, branch retinal artery occlusion, and severe vision loss. Am J Ophthalmol. 1999; 127: 223-4. **33.** Ormerod LD, Dailey JP. Ocular manifestations of cat-scratch disease. Curr Opin Ophthalmol. 1999; 10: 209-16. **34.** Wade NK, Po S, Wong IG, Cunningham ET Jr. Bilateral *Bartonella*-associated neuroretinitis. Retina. 1999;19: 355-6. **35.** Grando D, Sullivan LJ, Flexman JP, Watson MW, Andrew JH. *Bartonella* henselae associated with Parinaud's oculoglandular syndrome. Clin Infect Dis. 1999; 28: 1156-8. **36.** Rosen BS, Barry CJ, Nicoll AM, Constable IJ. Conservative management of documented neuroretinitis in cat scratch disease associated with *Bartonella* henselae infection. Aust N Z J Ophthalmol. 1999; 27:153-6. **37.** Dehio C. Interactions of *Bartonella* henselae with vascular endothelial cells. Curr Opin Microbiol. 1999; 2: 78-82. **38.** Gray AV, Reed JB, Wendel RT, Morse LS. *Bartonella* henselae infection associated with peripapillary angioma, branch retinal artery occlusion, and severe vision loss. Am J Ophthalmol. 1999; 127: 223-4. **39.** Rosen B. Management of B. henselae neuroretinitis in cat-scratch disease. Ophthalmology. 1999; 106: 1-2. **40.** Lee AG. Cat-scratch disease. Ophthalmology. 1999; 106: 1. **41.** Wade NK, Jones MR, Bhisitkul R, Fine L, Cunningham Jr ET. Optic disk edema associated with peripapillary serous retinal detachment: an early sign of systemic *Bartonella henselae* infection. Am J Ophth 2000;130: 327-334. **42.** Cunningham Jr ET, Koehler, JE. Ocular *Bartonella*. Am J Ophth 2000; 130: 340-349. **43.** Gabler B, Linde HJ, Reischl U, Lohmann CP. Disciform keratatis caused by *Bartonella* henselae infection: detection of a rare ocular complication of cat-scratch disease with PCR Klin Monatsbl Augenheilkd. 2000; 217: 299-302. **44.** Lohmann CP, Gabler B, Kroher G, Spiegel D, Linde HJ, Reischl U. Disciforme keratitis caused by *Bartonella* henselae: an unusual ocular complication in cat scratch disease. Eur J Ophthalmol. 2000;10: 257-8. **45.** Rost Monahan S. Neuroretinitis: a clinical syndrome of cat-scratch disease. Clin. Eye Vis. Care. 2000; 12: 155-159. **46.** Kerkhoff FT, Rothova A. *Bartonella* henselae associated uveitis and HLA-B27. Br J Ophthalmol. 2000; 84: 1125-9. 47. Shoham N, Miron D, Raz R, Garzozi HJ. Familial parinaud oculo-glandular syndrome in cat-scratch disease Harefuah. 2000 ;138: 1034-6, 1086. **48.** Lohmann CP,

Winkler von Mohrenfels C, Gabler B, Reischl U, Kochanowski B. Polymerase chain reaction (PCR) for microbiological diagnosis in refractory infectious keratitis: a clinical study in 16 patients. Klin Monatsbl Augenheilkd. 2000; 217: 37-42. **49.** Sobha S, Reck AC, Evans A. Neuroretinitis associated with cat scratch disease in a child. Clin Exper Ophth. 2000; 28: 127-8. **50.** Suhler EB, Lauer AK, Rosenbaum JT. Prevalence of serologic evidence of cat scratch disease in patients with neuroretinitis. Ophthalmology. 2000; 107: 871-6. **51.** Eggenberger E. Cat scratch disease: posterior segment manifestations. Ophthalmology. 2000; 107: 817-8. **52.** Gabler B, Linde HJ, Reischl U, Lohmann CP. Disciform keratatis caused by *Bartonella* henselae infection: detection of a rare ocular complication of cat-scratch disease with PCR. Klin Monatsbl Augenheilkd. 2000; 217: 299-302. **53.** Rost Monahan S. Neuroretinitis: a clinical syndrome of cat-scratch disease. Clin. Eye Vis. Care. 2000; 12: 155-159. **54.** Lohmann CP, Gabler B, Kroher G, Spiegel D, Linde HJ, Reischl U. Disciforme keratitis caused by *Bartonella* henselae: an unusual ocular complication in cat scratch disease. Eur J Ophthalmol. 2000; 10: 257-8. **55.** Shoham N, Miron D, Raz R, Garzozi HJ. Familial parinaud oculo-glandular syndrome in cat-scratch disease. Harefuah. 2000 Jun 15;138(12):1034-6, 1086. **56.** Chang MS, Lee SS, Cunningham ET Jr. Focal retinal phlebitis as a presenting sign of systemic *Bartonella* henselae infection. Retina. 2001; 21: 280-1. **57.** Bhatti MT, Asif R, Bhatti LB. Macular star in neuroretinitis. Arch Neurol. 2001; 58: 1008-9. **58.** Labalette P, Bermond D, Dedes V, Savage C. Cat-scratch disease neuroretinitis diagnosed by a polymerase chain reaction approach. Am J Ophthalmol. 2001;132 :575-6. 59. Dai S, Best S, St John M. *Bartonella* henselae neuroretinitis in cat scratch disease. N Z Med J. 2001; 114: 360-1. **60.** Messina F, Doria R, Gabriellini G, Sartini MS, Tascini C, Menichetti F. *Bartonella* henselae neuroretinitis. Clin Microbiol Infect. 2001; 7: 387-8. **61.** Canzano JC, Lim JI. Pars plana vitrectomy for epiretinal membrane secondary to cat scratch neuroretinitis. Retina. 2001; 21: 272-3. 62. Starck T, Madsen BW. Positive polymerase chain reaction and histology with borderline serology in Parinaud's oculoglandular syndrome. Cornea. 2002; 21: 625-7. **63.** Mirakhur B, Shah SS, Ratner AJ, Goldstein SM, Bell LM, Kim JO. Cat scratch disease presenting as orbital abscess and osteomyelitis. J Clin Microbiol. 2003; 41: 3991-3. **64.** Diaz-Valle D, Toledano Fernandez N, Arteaga Sanchez A, Miguelez Sanchez R, Pascual Allen D. Severe retinal phlebitis in ocular bartonellosis. Arch Soc Esp Oftalmol 2003;78: 223-6. **65.** Kobayashi K, Koga T, Oki T, Iwao K, Okumura A, Okinami S. Cat scratch disease with posterior segment involvement. Nippon Ganka Gakkai Zasshi 2003; 107: 99-104. **66.** Kotake S. Zoonosis and ocular diseases. Nippon Ganka Gakkai Zasshi. 2003; 107: 69-70. **67.** Haberl R, Wenisch C. Case 33-2002: a 28-year-old woman with ocular inflammation, fever, and headache. N Engl J Med 2003; 348: 474-6; author reply 474-6. **68.** Fukushima A, Yasuoka M, Tsukahara M, Ueno H. A case of cat scratch disease neuroretinitis confirmed by polymerase chain reaction. Jpn J Ophthalmol 2003; 47: 405-8. **69.** Chavkin MJ, Lappin MR, Powell CC, Cooper CM, Munana KR, Howard LH. *Toxoplasma gondii*-specific antibodies in the aqueous humor of cats with toxoplasmosis. Am J Vet Res 1994; 55: 1244-9. **70.** Lappin MR, Burney DP, Hill SA, Chavkin MJ. Detection of *Toxoplasma gondii*-specific IgA in the aqueous humor of cats. Am J Vet Res 1995; 56: 774-8. **71.** Lappin MR, Burney DP, Dow SW, Potter TA. Polymerase chain reaction for the detection of *Toxoplasma gondii* in aqueous humor of cats. Am J Vet Res 1996; 57: 1589-93.

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NEWSLETTER

Do *Bartonella* Cause Disease in Cats? I. Experimental Support©

Evelyn E. Zuckerman, Editor | Winter 2010 | Vol. 9, Number 1

In This Issue:

In the winter 2010 issue of the NVL Newsletter we will once again discuss the experimental evidence that *Bartonella* **DEFINITELY** cause disease in domestic cats. There is still continuing controversy regarding the pathogenicity of feline *Bartonella* in cats. Several academic feline clinicians and researchers on the VIN message boards and in scientific seminars, continue to question the ability of feline *Bartonella* to cause disease in domestic cats and to fulfill Koch's Postulates. There are 11 experimental studies, 6 of which show that *Bartonella* cause inflammatory diseases in many tissues in cats.[1-11]

Robert Koch in his laboratory

Koch's Postulates:

For more than 100 years science and medicine have relied on Koch's Postulates to determine the microbial cause of diseases.[12] In their simplest form, Koch's Postulates state: 1) Universal presence of the microbe, 2) Isolation of the microbe in pure culture, 3) Inoculation of the microbe into a susceptible host must recreate the disease, and 4) Observe the same disease and re-isolate the microbe in pure culture.

Introduction:

There is ample evidence that *Bartonella* cause inflammatory diseases in humans, dogs, and cats. Experimental inoculation of *Bartonella* in cats has been shown to cause inflammatory diseases in 6 of the 11 published studies.[1-6] Despite these publications several critics continue to insist, on VIN and in national lectures, that *Bartonella* do not cause disease in pet cats. In addition to these experimental studies there are publications of naturally occurring *Bartonella* diseases in pet cats which will be discussed in a future Newsletter.

There are 11 published studies of the experimental induction of *Bartonella* diseases in cats.

Experimental Studies:

There have been conflicting results from the 11 *Bartonella* experimental infection studies with regard to clinical signs and disease outcome (Tables 1 & 2).[1-11] Necropsy findings were reported in only 3 of the 11 studies and, in these publications, there is clear evidence of inflammatory disease occurring in most of the *Bartonella* inoculated cats. In the studies where necropsies were performed, evidence of inflammatory disease in the skin, lymph nodes, liver, spleen, muscle, heart and kidney were documented. In 5 of the 7 studies, where necropsies were not performed, no evidence of disease was noted. These discrepant results are difficult to compare because of different *Bartonella* strains used, infected blood versus pure *Bartonella* cultures used in some studies, different routes and size of inoculations used, the genetics of the cats used in the studies and variable use of necropsies.

There is solid experimental evidence (summarized in Tables 1 & 2) that *Bartonella* induce inflammatory diseases which fulfill Koch's Postulates.[12-13] The continuing controversy may boil down to semantics: is inflammation a disease or a "disease process?" Inflammation of the liver is the disease "hepatitis"; inflammation in the eye can be "uveitis or chorioretinitis". In addition, the critics continue to ask "how can *Bartonella* cause so many diseases?" *Bartonella* only cause one disease "process" which is inflammation that can occur in any tissue. Thus *Bartonella* are multi tissue pathogens which cause inflammation in numerous organ systems of cats, dogs and people.

Summary of Experimental Findings:

We have posted full text PDF files of the following experimental disease publications on our web site: www.natvetlab.com.

The first paper describing experimental *Bartonella* diseases was published by Greene et al. in 1996 where they found skin papules at the inoculation site and lymphadenopathy in 8 of the 8 inoculated cats.[1] In addition they found that proper long term high dose antibiotic therapy cleared the *Bartonella* infections. This observation, and a similar successful therapy of naturally infected cats by Koehler and her colleagues, have been overlooked by those who continue to say that therapy for *Bartonella* infection is not possible.[14]

Guptill and her colleagues reported, in 1997, a study with necropsy findings: 12 of 12 cats developed lymphadenopathy, 12 of 12 splenic follicular hyperplasia, 8 of 12 fever, 3 of 12 hepatitis and liver granulomas, 1 of 12 myocarditis, and 1 of 12 pyogranulomatous nephrtis.[2] Despite these observations, the authors stated "there are few or no clinical signs of disease." This is a case of subclinical disease in a group of SPF cats only observed for 8 months.

In 1999 Kordick and Breitschwerdt reported 13 of 13 inoculated cats developed lymphadenopathy, 9 of 13 splenic follicular hyperplasia, 9 of 13 cholangiohepatitis, 8 of 13 myocarditis, and 4 of 13 interstitial nephritis.[3] **They concluded "Detection of histologic changes in these cats supports a potential etiological role for *Bartonella* species in several idiopathic disease processes in cats."**

The last 2 studies that we will summarize were by O'Reilly and her colleagues.[4,5] They found overwhelming evidence that *Bartonella* cause disease in cats. In the first study, using various sources of *Bartonella* (pure culture, infected blood or infected flea feces), they found 17 of 17 cats developed fever and anorexia, 16 of 17 lymphadenopathy, 17 of 17 lethargy, 13 of 17 myalgia, 5 of 17 became aggressive.[4] They concluded that: "The LSU16 strain of *B. henselae* caused a reproducible clinically characteristic disease in cats. These signs are compatible with those reported for human patients with moderate to severe CSD." Their second study found that *Bartonella* induced lymphadenopathy, fever, and lethargy in all 9 kittens, neurological signs of aggression in 7 of 9, papules at the injection sites in 5 of 9, anorexia in 6 of 9, and myositis in 3 of 9 kittens.[5] They state "In this study reported here, *B. henselae* strain LSU16 causes reproducible, clinically characteristic disease in kittens." They suggest "Kittens that are febrile, anorectic, lethargic, and that have lymphadenopathy should be tested for *Bartonella* organisms, and contact with immunocompromised owners should be discouraged."

Editor's Note:

These studies conclusively demonstrate that *Bartonella* cause inflammatory disease processes in various tissues and organs in cats and that *Bartonella* infected cats can be treated successfully to eliminate their infections. It is time for the veterinary profession to end this controversy and get on with trying to prevent *Bartonella* diseases in cats and the zoonotic spread to people.[14-16]

Table 1

Bartonella Experimental Disease Studies (References 1-11)

Ref	Year	*Bartonella* Inoculum	Cat Inoculated: Source	Age	Length of Observation	Necropsy	Diseases Observed
Studies with Disease Induction:							
1	1996	*B. henselae*	Random Source	1-12 months	1 month	No	8/8 skin papules at inoculation site 8/8 lymphadenopathy
2	1997	*B. henselae*	SPF	3 months	8 months	Yes	12/12 lymphadenopathy 12/12 splenic follicular hyperplasia 8/12 fever 3/12 hepatitis & liver granulomas 1/12 myocarditis 1/12 pyogranulomatous nephritis
3	1999	*B. henselae*	SPF	4 months	15 months	Yes	13/13 lymphadenopathy 9/13 splenic follicular hyperplasia 9/13 cholangiohepatitis 8/13 myocarditis 4/13 interstitial nephritis
4	1999	*B. henselae*	SPF & Pound	7-15 months	2 months	No	SEE TABLE 2 BELOW
5	2000	*B. henselae* LSU 16 strain	SPF	3 months	6 months	Yes	9/9 fever 9/9 lymphadenopathy 9/9 lethargy 7/9 neurological signs- aggression 6/9 anorexia 5/9 skin papules at inoculation site 3/9 myositis
6	2001	*B. henselae* LSU 16 strain	SPF	10 months	2.5 months	No	6/6 skin lesions 4/6 fever
Studies without Disease Induction:							
7	1996	*B. henselae*	SPF	3-5 months	12 months	No	0/5 no clinical disease
8	1996	*B. henselae* Houston-1 strain	SPF	8 months	8 months	No	0*/31 no clinical disease * 2 skin swellings
9	1997	*B. henselae*	SPF	2-18 months	9 months	No	0/13 no clinical disease
10	2001	*B. henselae* Houston-1 strain	Random Source	Not specified	2-24 months	No	0/5 no clinical disease
11	2002	*B. koehlerae*	Random Source	10-12 months	6 months	No	0/4 no clinical disease

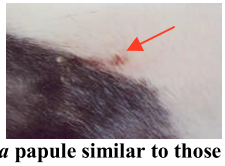
Table 2

Adverse clinical signs in cats inoculated with *B. henselae* (Strain LSU16)

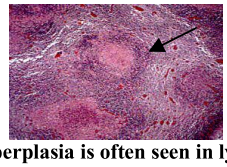
Reproduced from reference 4, O'Reilly et al.

Sign	No. of cats exhibiting sign/total no. (%) inoculated with[a]: Uninfected Controls	Pure culture LSU16	Infected blood	Infected flea feces
Fever[b]	0/15 (0%)	9/9 (100%)	3/3 (100%)	5/5 (100%)
Lethargy	0/15 (0%)	9/9 (100%)	3/3 (100%)	5/5 (100%)
Swelling and/or redness at inoculation site	0/15 (0%)	9/9 (100%)	3/3 (100%)	4/5 (80%)
Pustule at inoculation site	0/15 (0%)	3/9 (33%)	0/3 (0%)	0/3 (0%)
Anorexia	0/15 (0%)	9/9 (100%)	3/3 (100%)	5/5 (100%)
Anorexia requiring force feeding and/or fluids	0/15 (0%)	3/6 (50%)	0/3 (0%)	5/5 (100%)
Vomiting	0/15 (0%)	1/9 (11%)	0/3 (0%)	0/5 (0%)
Muscle pain or stiffness	0/15 (0%)	8/9 (89%)	2/3 (67%)	3/5 (60%)
Abnormal or aggressive behavior	0/15 (0%)	5/9 (56%)	0/3 (0%)	0/5 (0%)
Lymphadenopathy	7/15 (47%)	5/6[c] (83%)	3/3 (100%)	5/5 (100%)

[a] Number of cats that showed the indicated sign at any time in the study.
[b] Rectal temperature of >103.0°F (39.4°C).
[c] 3 cats receiving pure-culture were not monitored for lymphadenopathy during the first 4 weeks postinfection and were excluded.



***Bartonella* papule similar to those seen at experimental injection sites.**



Follicular hyperplasia is often seen in lymphoid organs of experimentally infected cats.

References:

1. Greene, CE, McDermott, M, Jameson, PH, Atkins, CL, and Marks, AM: *Bartonella henselae* infection in cats: evaluation during primary infection, treatment, and rechallenge infection. J Clin Microbiol 34:1682-1685, 1996.
2. Guptill L, *et al.* Experimental infection of young specific pathogen-free cats with *Bartonella henselae*. J Infect Dis 176:206-216, 1997.
3. Kordick DL et al.: Clinical and pathologic evaluation of chronic *Bartonella henselae* or *Bartonella clarridgeiae* infection in cats. J Clin Microbiol 37:1536-1547, 1999.
4. O'Reilly, KL *et al.*: Acute clinical disease in cats following infection with a pathogenic strain of *Bartonella henselae* (LSU16). Infect Immun 67:3066-3072, 1999.
5. Mikolajczyk MG, O'Reilly KL: Clinical disease in kittens inoculated with a pathogenic strain of *Bartonella henselae*. Am J Vet Res 61:375-379, 2000.
6. O'Reilly KL et al.: Passive antibody to *Bartonella henselae* protects against clinical disease following homologous challenge but does not prevent bacteremia in cats. Infect Immun 69:1880-1882, 2001.
7. Chomel, BB, *et al.* Experimental transmission of *Bartonella henselae* by the cat flea. J Clin Microbiol 34:1952-1956, 1996.
8. Regnery RL, *et al.* Experimentally induced *Bartonella henselae* infections followed by challenge exposure and antimicrobial therapy in cats. Am J Vet Res 57:1714-1719, 1996
9. Abbott RC, Chomel BB, Kasten, *et al.*: Experimental and natural infection with *Bartonella henselae* in domestic cats.Comp Immunol Microbiol Infect Dis 20:41-51, 1997.
10.. Zanutto MS, *et al.*: Experimental infection and horizontal transmission of *Bartonella henselae* in domestic cats. Rev Inst Med Trop S Paulo 43:257-261, 2001.
11. Yamamoto, K, *et al.*: Experimental infection of domestic cats with *Bartonella koehlerae* and comparison of protein and DNA profiles with those of other *Bartonella* species infecting felines. J Clin Microbiol 40:466-474, 2002.
12. Koch R.: Uber bakteriologische Forschung Verhandlung des X Internationalen Medichinischen Congresses, Berlin, 1890, 1, 35. August Hirschwald, Berlin. (In German.) Xth International Congress of Medicine, Berlin, 1981.
13. Jacomo, V., Kelly, P.J. Raoult, D. Natural history of *Bartonella* infections (an exception to Koch's Postulate). Cl. Diag. Lab. Immunol. 9: 8-18, 2002.
14. Koehler JE, Glaser CA, Tappero JW: *Rochalimaea henselae* infection: a new zoonosis with the domestic cat as reservoir. JAMA 271:531-535, 1994..
15. Hardy, WD, Jr., Zuckerman, E, Corbishley, J. Seroprevalence of *Bartonella*-infection in healthy and diseased cats in the United States and Caribbean: Evidence for *Bartonella*-induced diseases in cats. Internat Conf American Society for Rickettsiology, Big Sky, Montana, August 17-22, 2001.
16. Hardy, WD, Jr., Zuckerman, EE, Corbishley, J, Gold, JWM[3], Baron, P, Polsky, B, Gilhuley, K, Kiehn, TE, and Armstrong, DA. Efficacy of high dose, long duration Doxycycline or Azithromycin treatment for *Bartonella* infections in pet cats. International Conference of the American Society for Rickettsiology, Big Sky, Montana, August 17-22, 2001.

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NEWSLETTER

Do *Bartonella* Cause Disease in Cats? II. Evidence from Pet Cats©

Evelyn E. Zuckerman, Editor **Spring 2010** **Vol. 9, Number 2**

In This Issue:

In the spring 2010 issue of the NVL Newsletter we will continue to present published evidence that *Bartonella* do, in fact, cause inflammatory diseases in pet cats. Our last newsletter reviewed studies of experimentally-induced *Bartonella* diseases in cats and we will now review publications that document the same in pet cats.

Conclusion:

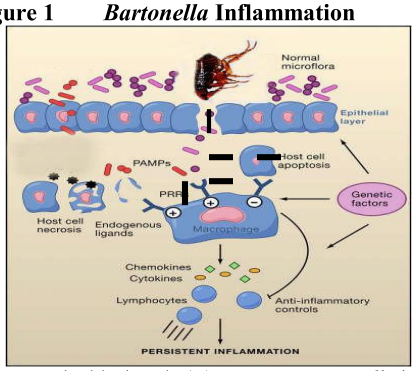
Bartonella cause disease in pet cats:

1. *Bartonella* induce inflammatory diseases after experimental inoculation.
2. Koch's Postulates have been fulfilled.
3. *Bartonella* cause inflammatory diseases in pet cats.
4. *Bartonella* infection in pet cats can be eliminated by antibiotic therapy and can be confirmed by a post therapy comparative antibody titer reduction test.

Bartonella Pathogenesis:

Bartonella stick or clump together in tissues and stick to, and penetrate, RBCs, macrophages, and capillary endothelial cells. Pili, hair-like structures found on the bacteria's surface, and a protein called deformin, are responsible for the sticky properties.[1] The ability to adhere to many cell types leads to the wide and varied tissue pathogenesis observed in cats, dogs, and people. In addition, *Bartonella* stimulate macrophages and other cells to produce cytokines which orchestrate the inflammatory process (Figure 1).

Figure 1 *Bartonella* Inflammation



Legend: The black rods (--) represent *Bartonella* in the tissues. The bacteria induce an outpouring of inflammatory cytokines which recruit inflammatory cells such as lymphocytes, plasma cells, and macrophages. Adapted from reference 2.

Publications of *Bartonella* Diseases in Pet Cats:

Does coinfection of *Bartonella henselae* and FIV induce clinical disorders in cats? Ueno, H., Hohdatsu, T., Muramatsu, Y., and Morita, C. Microbiol Immunol 40: 617-620, 1996.

This group of Japanese veterinarians found a causal association of *Bartonella henselae* with gingivitis and lymphadenopathy in a study of 170 pet cats. They found that *Bartonella henselae* may induce clinical disorders in pet cats from a comparison of the serological status for *Bartonella henselae* with the serological status for feline immunodeficiency virus (FIV) and several clinical diseases. Seropositivity for *Bartonella henselae* was not significantly different between FIV antibody-positive and -negative cats (18.4% vs. 16.0%). Clinical diseases were compared among four groups of cats distinguished by the reactivity of sera against *Bartonella henselae* and FIV. The incidence of lymphadenopathy was lower in only FIV antibody-positive cats (3.0%), but higher in *Bartonella henselae* antibody-positive cats (13.6%) and significantly higher in both *Bartonella henselae* and FIV antibody-positive cats (42.9%) compared with the incidence of lymphadenopathy in cats which were negative for both antibodies (5.5%). The same relationship was also observed for the incidence of gingivitis among the 4 cat groups, suggesting that coinfection of *Bartonella henselae* and FIV may be associated with gingivitis and lymphadenopathy in cats.

Seroprevalence of *Bartonella henselae* infection and correlation with disease status in cats in Switzerland. Glaus, T., Hofmann-Lehmann, R., Greene, C., Glaus, B., Wolfensberger, C., and Lutz, H.: J Clin Microbiol 35:2883-2885, 1997.

The authors reported a low seroprevalence for *Bartonella henselae* in 728 cats living in Switzerland, which is not a geographic area known to be favorable for flea habitation, the major *Bartonella* vector. They found a seroprevalence of only 8.3% for all cats and did not find any significantly different prevalence between sick and healthy cats (9.2 versus 7.2%). However, in sick cats seropositive for *Bartonella henselae*, they found an increased frequency of stomatitis (P=0.0117) and a variety of diseases of the kidneys and the urinary tract that were not further differentiated (P=0.0337).

Vegetative endocarditis in six cats. Malik, R, Barrs, VR, Church, DB, Zahn, A, Allan, GS, Martin, P, Wigney, DI, and Love, DN. J Feline Med Surg 1:171-180, 1999.

This paper describes 6 cases of vegetative endocarditis in Australian cats. Two of the cases were caused by *Bartonella* species isolated from the blood. The first case occurred in a 9-year-old DSH cat with a history of chronic dermatitis. On presentation there was a loud systolic murmur, cardiomegaly, pleural effusion and dyspnea. Echocardiography demonstrated thickened aortic valves. Despite therapy, the cat died of heart failure and the owners refused a necropsy. The second case occurred in a six year-old Persian cat who presented with severe dyspnea, hypertrophic cardiomegaly and pericardial effusion. The cat died 11 months later and necropsy revealed vegetative lesions on the aortic and mitral valves. Even though *Bartonella* were cultured from the blood of these 2 cats, the authors did not attempt to identify *Bartonella* in the vegetative valvular lesions.

Seroprevalence of *Bartonella*-infection in healthy and diseased cats in the United States and Caribbean: Evidence for *Bartonella*-induced diseases in cats. Hardy, WD, Jr., Zuckerman, E, Corbishley, J. Internat. Conf. Amer. Society for Rickettsiology, Big Sky, MT, August 17-22, 2001. In 2001, we reported the association of *Bartonella* with numerous inflammatory diseases in pet cats, oral and ocular disease being most common (Figures 2 & 3).

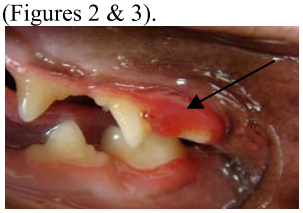


Figure 2. Early proliferative gingivitis in a young cat with no tartar. *Bartonella* seropositive +4 WB cat.

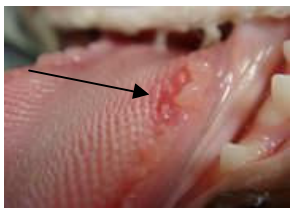


Figure 3. Oral ulcers on the tongue of a *Bartonella* seropositive +4 WB cat. Courtesy: Jan Corbishley, VT, Oradell Animal Hospital, Paramus, NJ.

We noted that the inflammatory diseases often occurred simultaneously in several tissues (Figure 4) such as the oral cavity and the eye or the respiratory tract and the skin.[3] Confirmation that *Bartonella* were the cause of these diseases was the significant clinical improvement after *Bartonella* antibiotic therapy and the corollary decrease in the *Bartonella* antibody titer.[4,5]

Figure 4. Concurrent gingivitis and keratitis in a *Bartonella* seropositive +3 WB cat. Courtesy: Dr. Maria Berger, Cat Clinic North, Grand Rapids, MI.

***Bartonella* spp antibodies and DNA in aqueous humor of cats.** Lappin, MR, Kordick, DL, and Breitschwerdt, EB. J Feline Med Surg 2:61-68, 2000.
This group studied 49 client owned pet cats and 49 healthy shelter cats for the association of *Bartonella* and ocular infection. They detected *Bartonella* spp IgG (C value >1) in 7 of 49 pet cats with uveitis but in none of the healthy 49 shelter cats. They concluded: "*Bartonella* spp infect the eyes of some cats following natural exposure or experimental inoculation and may cause uveitis in some cats."
Editors Note: Our data show a very strong association of *Bartonella* and uveitis and other ocular inflammatory diseases including chorioretinitis, glaucoma and conjunctivitis.[6,7]

Fatal case of endocarditis associated with *Bartonella henselae* type I infection in a domestic cat. Chomel, BB, Wey, AC, Kasten, RW, Stacy, BA, and Labelle, P. J Clin Microbiol 41:5337-5339, 2003.
This case occurred in an 8-year-old female spayed cat who presented with a grade IV/VI systolic heart murmur and an arrhythmia. Thoracic radiographs revealed severe cardiomegaly and an echocardiogram showed markedly thickened aortic valve leaflets. Blood culture at this time, and 1 month later, were negative even though there was high antibody titers to *Bartonella henselae* (1:4,096) and *Bartonella clarridgeiae* (1:8,192). The cat died due to cardiopulmonary arrest despite resuscitation attempts. Necropsy revealed *Bartonella henselae* Type I DNA and silver stain positive coccoid structures in endothelial cells of the damaged aortic valve.
Editors Note: This case demonstrates that *Bartonella* specific antibodies can be present even when the bacteria cannot be cultured from the blood.[3] It has been shown that *Bartonella* infected cats have intermittent bacteremia which may account for the inability to culture the bacteria from the blood of some antibody positive infected cats.[8]

A new etiological agent of feline ocular diseases. Ketring, KL, Zuckerman, EE & Hardy, WD, Jr. *Bartonella*: JAAHA, 40:6-12, 2004.
In 2004, Dr. Kerry Ketring and our laboratory published the association of *Bartonella* with feline ocular diseases. We studied 1,649 cases of ocular inflammation in pet cats, many seen by Dr. Ketring, a Diplomat, ACVO. We reported the association in: uveitis 145/251 58%, conjunctivitis 704/1,375 51%, chorioretinitis 6/7 86%, keratitis 3/4 75% and corneal ulcer 7/12 58%. Thus 872/1,649 53% of cats with ocular inflammatory diseases were seropositive for *Bartonella* by western blot. Notably, in most of these cats, there was marked clinical improvement or total resolution of their disease with azithromycin antibiotic therapy (Figure 5).

Figure 5. Corneal Ulcer: Before and after therapy[6]

Recurrent osteomyelitis in a cat due to infection with *Bartonella vinsonii* subsp. *berkhoffii* genotype II. Varanat, M, Travis, A, Lee, W, Maggi, RG, Bissett, SA, Linder, KE, and Breitschwerdt, EB. J Vet Intern Med 23:1273-1277, 2009.
This is a case report of a 4-year-old spayed-female DSH cat who originated from a North Carolina shelter as a kitten. There was a nonpainful swelling of the left metatarsal region which showed lysis of the 1st metatarsal bone by radiographs. The left metatarsophalangeal joint was disarticulated and the digit was removed. The disease recurred a year later and at that time direct *Bartonella* PCR from the blood was negative whereas *Bartonella* DNA was amplified from blood culture media even though there was no bacterial growth and the *Bartonella vinsonii* subsp. *berkhoffii* antibody titer was positive at 1:128. The cat was treated for 3 months with azithromycin at 10 mg/kg PO q48h. The cat's condition improved and 6 months after therapy no *Bartonella* were cultured from the blood and the antibody titer decreased to negative.
Editors Note: There are 7 *Bartonella* species that infect pet cats. As we have reported for 10 years, *Bartonella* infections can be eliminated by azithromycin antibiotic therapy and confirmed by a post therapy titer decrease.[4,5]

Association between *Bartonella* infection and disease in pet cats. Sykes, JE, Westropp, JL, Kasten, RW, and Chomel, BB. Abstract A1. Intern Conf on *Bartonella* as Medical & Veterinary Pathogens, Chester, UK, June 2009. In this study, 299 cats were evaluated for *Bartonella* associated diseases. They found a statistical association with *Bartonella* isolation and stomatitis (P=0.003).

"Negative" Publications of *Bartonella* Associated Diseases

There have been several publications reporting no association of *Bartonella* with diseases in pet cats.[9-11] Most of the studies compared the difference between healthy cats and cats with various diseases and used statistical analysis to show no association. Similar conclusions had been made for years for the lack of disease-association of *Helicobacter pylori* and human gastric ulcers and gastric cancer. Eventually these negative studies were proven incorrect and the elucidation of the pathogenesis of *H. pylori* led to the 2005 Nobel Prize in Medicine awarded to Barry J. Marshall and J. Robin Warren. The press release of the Nobel Assembly stated: "Many diseases in humans such as Crohn's disease, ulcerative colitis, rheumatoid arthritis, and atherosclerosis are due to chronic inflammation. The discovery of *Helicobacter pylori* has led to an increased understanding of the connection between chronic infection, inflammation, and cancer." *Bartonella* infection in cats leads to chronic inflammatory diseases similar to those of *H. pylori*.

P-Value Statistics- "Negative Studies"

The misuse of "statistical significance" in studies using inadequate numbers has been argued in the scientific literature for some time.[12,13] A relevant article was published in the British Medical Journal in 1995 by Altman and Bland entitled: **Absence of evidence in not evidence of absence.** The authors pointed out the common misuse of the "P-value" in publications, especially when the sample size studied was relatively small. Unlike those studies, we have tested more than 243,000 pet cats for *Bartonella* and found an association with inflammatory conditions in many tissues of pet cats.

References:

1. Xu, YH, Lu, ZY & Ihler, GM. Purification of deformin, an extracellular protein synthesized by *Bartonella bacilliformis* which causes deformation of erythrocyte membranes. Biochim Biophys Acta 1234: 173-83, 1995.
2. Karin, M, Lawrence, T, Nizet, V. Innate immunity gone awry: linking microbial infections to chronic inflammation and cancer. Cell 124:823-835, 2006.
3. Hardy, WD, Jr., Zuckerman, E, Corbishley, J. Seroprevalence of *Bartonella*-infection in healthy and diseased cats in the United States and Caribbean: Evidence for *Bartonella*-induced diseases in cats. International Conference of the American Society for Rickettsiology, Big Sky, MT, August 17-22, 2001.
4. Hardy, WD, Jr., Zuckerman, EE, Corbishley, J, *et al.* Efficacy of high dose, long duration Doxycycline or Azithromycin treatment for *Bartonella* infections in pet cats. International Conference of the American Society for Rickettsiology, Big Sky, Montana, August, 2001.
5. Hardy, W.D., JR., Zuckerman, E.E., Corbishley, J. *et al.* Successful therapy of *Bartonella henselae* bacteremic healthy pet cats. Annual Meeting, Infectious Disease Society of America, New Orleans, Sept., 1996.
6. Ketring, KL, Zuckerman, EE & Hardy, WD, Jr. *Bartonella*: A new etiological agent of feline ocular diseases. JAAHA, 40:6-12, 2004.
7. Hardy, WD, Jr., Zuckerman, E, Ketring, K, Fischer, C, Mineo, M. *Bartonella*-induced ocular inflammatory diseases of cats. Upsala J Med Sci, Suppl. 57: 37, 2005.
8. Kordick DL et al.: Clinical and pathologic evaluation of chronic *Bartonella henselae* or *Bartonella clarridgeiae* infection in cats. J Clin Microbiol 37:1536-1547, 1999.
9. Pearce LK, Radecki, SV, Brewer, M, and Lappin, MR. Prevalence of *Bartonella henselae* antibodies in serum of cats with and without clinical signs of central nervous system disease. J Feline Med Surg 8:315-320, 2006.
10. Berryessa, NA, Johnson, LR, Kasten, RW, and Chomel, BB. Microbial culture of blood samples and serological testing for bartonellosis in cats with chronic rhinosinusitis. JAVMA 233:1084-1089, 2008.
11. Quimby, JM, Elston, T, Hawley, J, Brewer, M, Miller, A, and Lappin, MR. Evaluation of the association of *Bartonella* species, feline herpesvirus 1, feline calicivirus, feline leukemia virus, and feline immunodeficiency virus with chronic feline gingivostomatitis. J Feline Med Surg 10:66-72, 2008.
12. Rigby, AS. Statistical methods in epidemiology. I. Statistical errors in hypothesis testing. Disability and Rehabilitation 20:121-126, 1998.
13. Altman, DG and Bland, JM. Absence of evidence is not evidence of absence. British Med J 311:485, 1995.

***Bartonella* references can be obtained at:**
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Bartonellosis: Cat Scratch Disease and Sequelae©

Evelyn E. Zuckerman, Editor **Fall 2010** **Vol. 9, Number 4**

In This Issue:

In the fall 2010 issue of the NVL Newsletter we will review human Bartonellosis- *Bartonella* diseases, CSD and sequelae, caused by *Bartonella* derived from cats and dogs. On PubMed, there are presently 3,416 *Bartonella* publications including several articles describing unusual sequelae of muscle and neurological complications of *Bartonella* infection in humans.

The Feline *Bartonella* Literature:

Healthy People:

At present there are 30 named *Bartonella* species and 3 subspecies.[1] *Bartonella* are mainly transmitted to mammalian reservoir host species via arthropod ectoparasite vectors such as fleas, ticks, lice and biting flies. An excellent review of the worldwide distribution of the 30 *Bartonella* species was recently published.[1] Interestingly and fortunately, *Bartonella bacilliformis*, the most deadly human *Bartonella* species, is confined to regions of high altitudes of South America, probably due to the restricted range of it's arthropod vector, the sand fly.[2] Untreated cases of *Bartonella bacilliformis* infections in the Andes mountains have a very high mortality of 30%.[2] However, worldwide *Bartonella henselae* is the most common species found in cats, dogs and humans.

Many publications state that "Species of *Bartonella*, which are vector-borne pathogens, cause persistent and asymptomatic bacteremia in their natural hosts."[1] However, there is ample evidence that this is not always the case. For example, *Bartonella bacilliformis* causes Oroya fever and many deaths in humans, the only known natural reservoir host for this species. In addition, there are many publications demonstrating that *Bartonella henselae* in cats and dogs and *Bartonella vinsonii* in dogs cause inflammatory diseases in these "natural host" reservoir species. Such statements have initiated controversy for the past 20 years in veterinary medicine and have caused many veterinary practitioners to dismiss the veterinary and public health importance of *Bartonella* infections in pet animals.

Several papers from China, Japan, Asia, Australia and Jordan report relatively high human *Bartonella* seroprevalence indicating possible current or past infections. In mainland China, Sun and colleagues report 19.6% seropositivity in healthy individuals from 8 areas of Zhejiang Province of eastern China.[3] The range was 32% in Hangzhou to 2% in Jiangshan. Interestingly, the seropositivity was highest for people exposed to dog, rather than cat, bites compared to healthy blood donors. Another publication from Taiwan found 1.7% of 295 healthy veterinary professionals to be seropositive for *Bartonella*.[4] In Japan, 129 veterinary students were tested for *Bartonella* antibody and 10.9% were positive.[5] Another Japanese study of veterinary professionals found 35 of the 233 (15%) were seropositive and females were twice as likely as males to have antibodies. Veterinary assistants and animal groomers were at highest risk.[6] In Thailand, 9 of 163 (5.5%) healthy individuals were seropositive for antibodies to *B. henselae*.[7] Finally, 53 of 482 (11%) healthy Jordanian children were seropositive to *B. henselae*.[8] Children 7-10-years were more likely to be seropositive than younger or older ones.

Editor's Note: Worldwide, cats and dogs are the most common animals that live in close contact with humans. This is probably why the most widely distributed *Bartonella* species in the world is *Bartonella henselae*, since cats and dogs serve as the "natural host" reservoir. Cat fleas are the most common flea species that infest cats and dogs which results in the transmission of *Bartonella henselae* from these pets to humans.

***Ctenocephalides felis*- the cat flea**

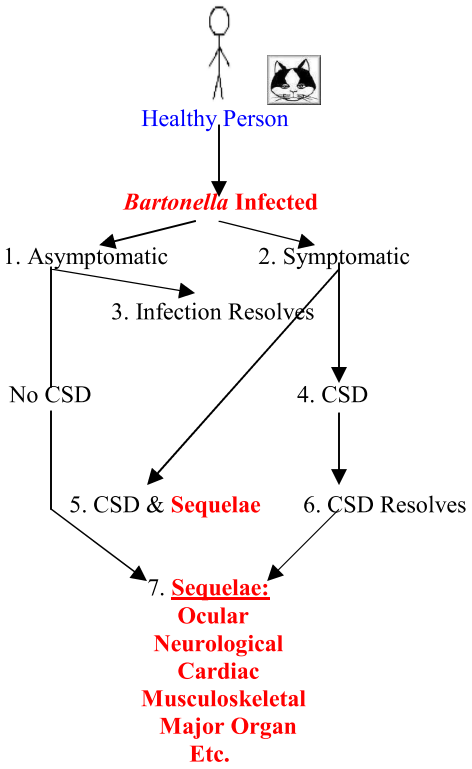
Human *Bartonella* Diseases:

Cat Scratch Disease (CSD):

All *Bartonella* diseases are not cat scratch disease (CSD) (Figure 1). CSD is the prototypical *Bartonella* disease but, in fact, may only represent about 50% of the clinically evident *Bartonella* diseases. CSD is characterized by a prodrome (the earliest consistent sign of a disease) of fever (usually prolonged or intermittent), a papule at the scratch or bite site, and lymphadenopathy.

Most physicians and veterinarians are familiar with classical CSD but are not often familiar with the sequelae that also occur (Figure 1). Sequelae are defined as conditions that follow as a consequence of a disease or infection and may remain long after the initiating disease or infection. An example of a common disease sequela is rheumatic fever following untreated Strep-throat infection of children.

Figure 1. **Bartonellosis**

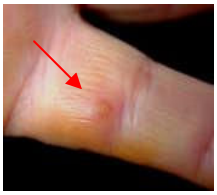


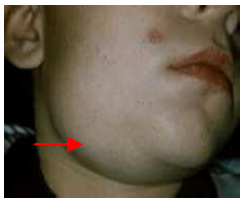
Bartonellosis and CSD have many sequelae including neurologic inflammatory disease, psychotic and cognitive disorders, ocular, heart, musculoskeletal and major organ inflammatory conditions. Thus, CSD may be envisioned as only the tip of the "*Bartonella* disease iceberg."

Figure 1 (stages 1 through 7) gives the possible outcomes of human infection with feline *Bartonella*. A healthy person who becomes infected after contact with a cat may remain asymptomatic (1) and her or his infection may resolve (3). However, an infected healthy person may become symptomatic within 1 to 6 weeks and develop classical CSD with fever, a papule and lymphadenopathy (2). CSD will resolve, without therapy, in 80% of people (6), however, about 20% will develop sequelae after the resolution of CSD (7). Some symptomatic

patients develop classic CSD and sequelae at essentially the same time (5). Similarly, some infected asymptomatic individuals will develop only sequelae weeks after their infection (7). These individuals are difficult for physicians since they present with symptoms different from classical CSD and often there is no mention of cat contact in the patient's history.

Classic CSD:


Papule on finger


Cervical lymphadenopathy

Bartonella Sequelae:

The sequelae of *Bartonella* infection and or CSD can involve any tissue in the body since *Bartonella* infect endothelial cells of capillaries. The following recent publications describe unusual sequelae of bartonellosis.

Unknown fever and back pain caused by *Bartonella henselae* in a veterinarian after a needle puncture: A case report and literature review. Lin, J-W, Chen, C-M and Chang, C. Vector-Borne & Zoonotic Dis., 2010.
This is a case report of a 32 year old male veterinarian working in a private veterinary clinic in Taiwan who developed intermittent fever and back pain for 1 month following a needle puncture to his right thumb while preparing medications. No scratch or bite from a cat or dog was reported before the illness began. The back pain was more severe during the periods of fever and he developed a right axillary lymphadenopathy. Blood cultures were sterile, initial PCR tests were negative but the IFA serological tests for IgG, at a 2 week interval, were positive at extremely high titers (1:131,072 and 1:65,536, respectively). An additional dot-blot PCR test was positive for *Bartonella henselae*. The patient was treated with ceftriaxone, doxycycline and azithromycin and recovered rapidly without recurrence. This is an unusual route of transmission by the presumed needle puncture and reinforces the increased risk to veterinary professionals for *Bartonella* zoonoses.

Neuralgic amyotrophy associated with *Bartonella henselae* infection. Stek, CJ. et al. J. Neurosurg. Psychiatry doi:10.1136/jnnp .2009 .191940, 2010 published online.
This is a report of 3 patients with brachial plexus neuropathy diagnosed as neuralgic amyotrophy (NA) that occurred after *Bartonella henselae* infection. NA is a debilitating disease of the brachial plexus characterized by severe shoulder and arm pain with weakness and loss of sensation. The exact cause is not yet understood but there is evidence of an immune cause. The evidence is inflammation in the brachial plexus, the presence of antiganglioside antibodies, and immune-triggering events, mostly infections, preceding the development of NA. Eleven viruses, 13 bacteria, and 1 fungus have been shown to precede the development of NA. The majority of the microorganisms, now including *Bartonella*, are intracellular organisms that are known to trigger a CD+ T cell-mediated immune response which implies a role for T-cell-mediated auto-immunity as the cause of NA.

The 3 patients described in this report were middle-aged men and all lived with cats. The first patient was 48 years old and developed CSD with fever for 1 month, lymphadenopathy and necrotizing liver granulomas. He was serologically positive but PCR negative in liver biopsy tissue for *Bartonella henselae*. Six weeks after the development of CSD the sequelae of acute severe pain in the left shoulder followed by weakness in that arm occurred. There was no mention of antibiotic therapy but the patient gradually recovered over several months.

The second patient was 53 years old and developed CSD with a painful swelling near the left elbow that progressed over 1 year into recurrent abscesses and suppurative axillary lymphadenopathy. Cultures were sterile but PCR and serology were positive for *Bartonella henselae.* A year later the sequela of NA occurred characterized by severe pain in the arm that radiated to several fingers followed by weakness in the right arm, the opposite arm from the original lymphadenopathy. Although no therapy was discussed in the paper, the patient regained full strength in his arm 1.5 years after the initial symptoms of NA.

The third patient was 46 years old who was hospitalized due to sudden severe pain and loss of strength (paresis) in both shoulders and arms. One week earlier he developed signs of CSD with fever, and a painful lymphadenopathy in his groin. He was serologically and PCR positive for *Bartonella henselae* on lymph node tissue. After treatment with rifampin and doxycycline, the inflammation in his groin and fever resolved. However, he still had pain and paresis and was unable to work for 1.5 years.

Expressive aphasia as a presentation of encephalitis with *Bartonella henselae* infection in an immunocompetent adult. Marienfeld, CB, et al. Yale J. Biol & Med. 83:67-71, 2010.
This case report describes severe neurological sequelae that developed in a 59 year-old man. Shortly after adopting several stray kittens he developed classic CSD with a skin papule and right axillary lymphadenopathy for which he was treated with a 5 day course of doxycycline. Ten days later he presented with sudden onset of speech difficulties and a 4mm papule on his right forearm. On neurological examination, he had expressive aphasia (difficulty communicating verbally), word substitution errors, and impaired repetition. An EEG showed moderate generalized slowing but no epileptiform activity. He became more confused as the aphasia fluctuated from paraphasic errors (using wrong words) and expressive aphasia. Then, 18 hours after the onset of symptoms, he had a generalized tonic-clonic seizure. He was negative for HSV, VZV, Enterovirus by PCR, Lyme and West Nile serology, and VDRL and CSF cultures were sterile. The next day his level of alertness worsened and he was aphasic and febrile. Because of the history of stray kittens and the skin papule and lymphadenopathy, the patient was tested for *Bartonella henselae* antibodies. His IgG and IgM titers were high (IgG 1:1,024 and IgM 1:20) and diagnostic. He was treated intravenously with 500mg of Azithromycin. There was an immediate improvement as reported: "The next morning, the patient's symptoms and aphasia had resolved." He was then discharged and switched to doxycycline and rifampin for 14 days. The patient has fully recovered as evidenced by this evaluation: "Today, the patient has resumed his occupation as a musician, singer, and songwriter. He is teaching classes and currently in the recording studio working on an album."

Patients older than 50 years of age with similar symptoms are often thought to have had strokes. These authors caution that when stroke has been eliminated from the diagnosis, *Bartonella* infection should be considered in the differential diagnosis. In this regard, between 0.17 and 2% of *Bartonella* infected patients develop the neurologic sequela of encephalopathy.[9, 10]

Summary:

These reports show that severe sequelae may follow the development of CSD. *Bartonella*, like other intracellular pathogens, may initiate immune attack of patient's tissues and lead to chronic debilitating disease long after the onset of infection and often after the infection has resolved. It is clear that *Bartonella* sequelae are far more severe than the clinical entity known as CSD. Veterinarians should take the lead in educating the public on the dangers of feline *Bartonella* zoonoses.

References:

1. Saisongkorh, W, et al. Emerging *Bartonella* in humans and animals in Asia and Australia. J. Med. Assoc. Thai. 92:707-731, 2009.
2. Ihler, GM. *Bartonella bacilliformis*: Dangerous pathogen slowly emerging from a deep background. FEMS Microbiol. Lett. 144: 1-11, 1996.
3. Sun, J., et al. Seroprevalence of *Bartonella* in Eastern China and analysis of risk factors. BMC Infectious Diseases 10:121-124, 2010.
4. Chang, C., et al. Cat-scratch disease in veterinary-associated populations and in its cat reservoir in Taiwan. Vet.Res. 37: 565-577, 2006.
5. Maruyama, K.E. et al. Serological investigation of *Bartonella henselae* infections in clinically cat-scratch disease-suspected patients, patients with cardiovascular diseases, and healthy veterinary students in Japan. Microbiol. Immunol. 46:313-316, 2002.
6. Kumasaka, K., et al. Survey of veterinary professionals foe antibodies to Bartonella henselae in Japan. Rinsho Byori. 49:906-910, 2001.
7. Maruyama, S., et al. Seroprevalence of *Bartonella henselae* and *Toxoplasma gondii* among healthy individuals in Thailand. J.VetMed.Sci.62:635-37, 2000.
8. Al-Majali, A.M. & Al-Qudah, K.M. Seroprevalence of *Bartonella henselae* and *Bartonella quintana* infections in children from central and northern Jordan. Saudi Med. J. 25:1664-1669, 2004.
9. Murakami, K., et al. Cat scratch disease: analysis of 130 seropositive cases. J Infect Chemother. 8:349-52, 2002.
10. Carithers, HA. Cat-scratch disease: an overview based on a study of 1,200 patients. Am J Dis Child. 139:1124-33, 1985.