BARTONELLA:

FELINE DISEASES AND EMERGING ZOONOSIS

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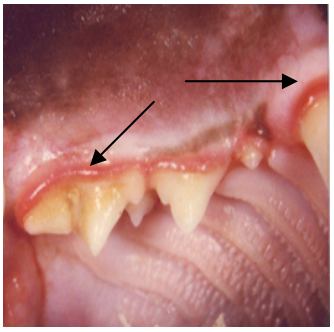

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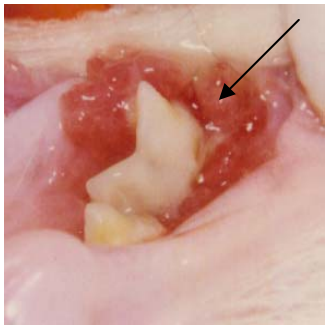

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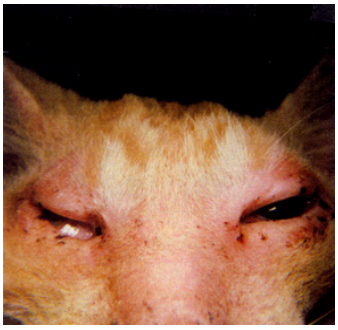

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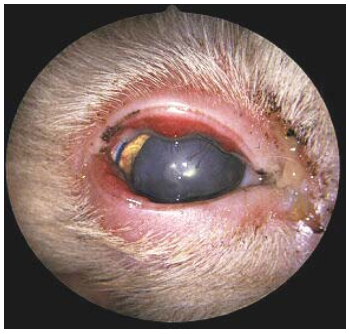

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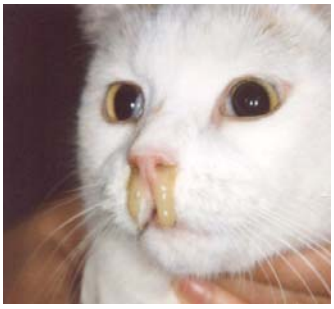

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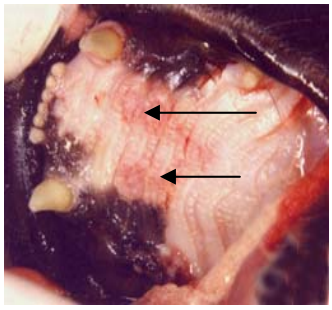

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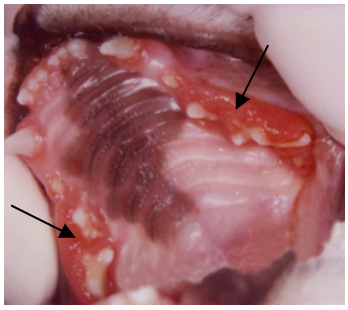
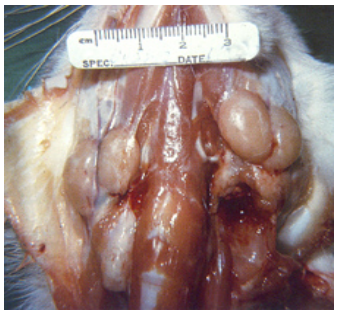


Stomatitis



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

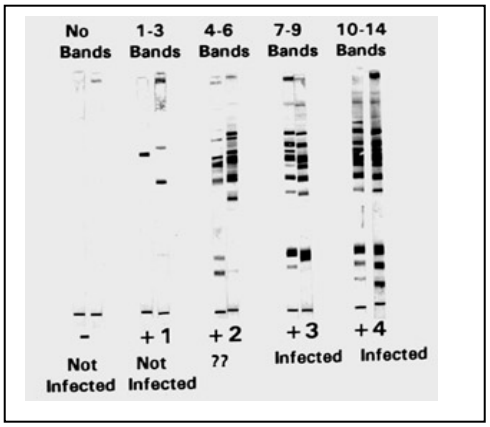
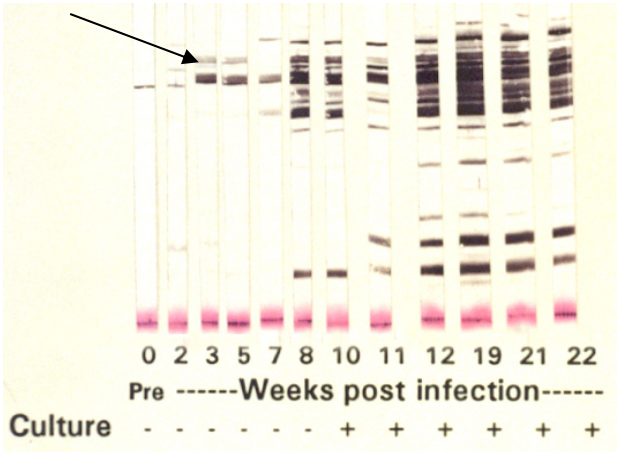


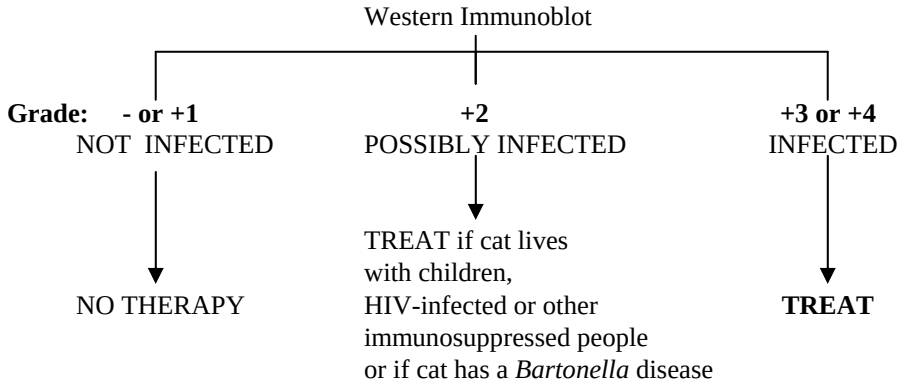
Figure 3 **SEROCONVERSION OF A CAT INFECTED BY BLOOD DONATION WITH *B. HENSELAE***



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.

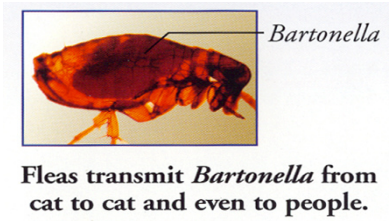
Figure 4

***BARTONELLA* SEROLOGY ALGORITHM**



Prevalence of *Bartonella* Infection in Cats:

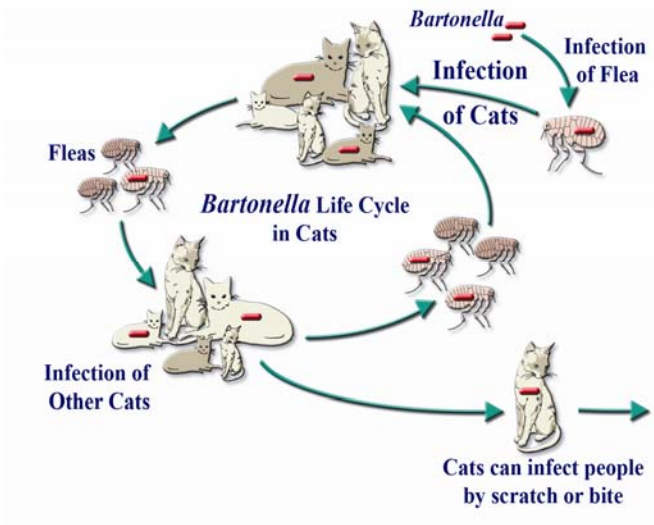
Healthy pet cats can carry five *Bartonella* species: *Bartonella henselae*, *Bartonella clarridgeiae*, *Bartonella koehlerae* *Bartonella elizabethae* and *Bartonella weissii*, in their blood. Most infected cats are healthy, inapparent carriers of these bacteria for years. It is not known if infected 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

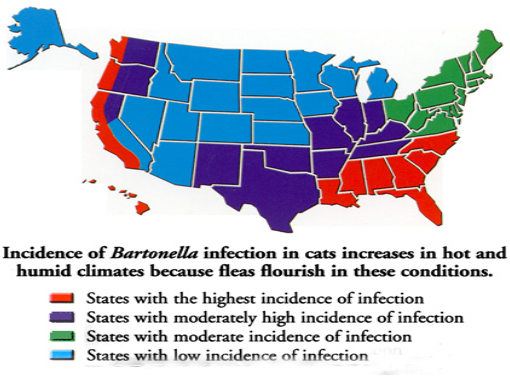


Table 3

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.

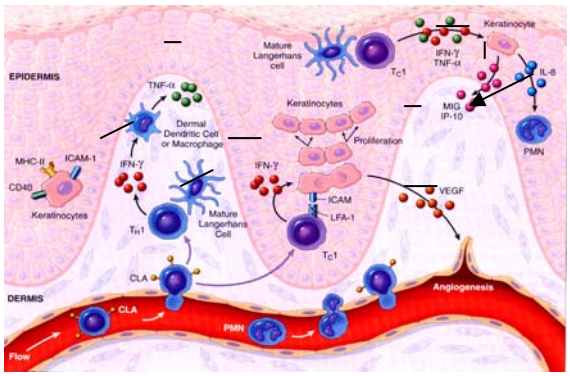


Figure 7 *Bartonella* Inflammation

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*

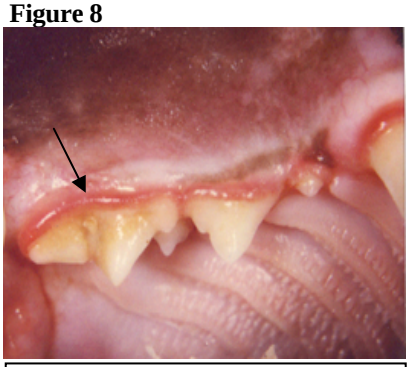
Oral Disease	No. Tested	No. Positive	% Positive	Difference
HEALTHY- NO KNOWN RISK FACTORS	**840**	**170**	**20%**	**X**
Gingivitis	**21,338**	**10,107**	**48%**	**2.4X**
Stomatitis	**1,350**	**760**	**56%**	**2.8X**
Oral Ulcers	**246**	**129**	**52%**	**2.6X**
Oral Disease Totals:	**22,934**	**10,996**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

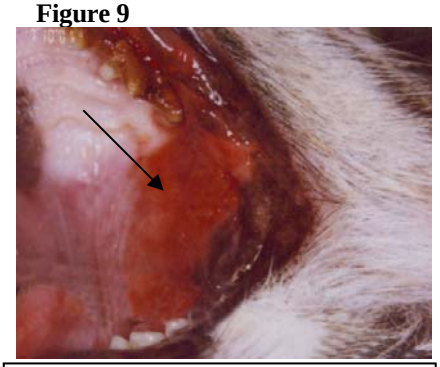
There is no distinct clinical or pathological presentation of *Bartonella*-seropositive oral diseases compared to oral diseases caused by other pathogens. Clinical parameters range from slight to very severe, including total mouth extractions (Figure 8, 9 & 10). The pathological parameters of *Bartonella*-seropositive 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



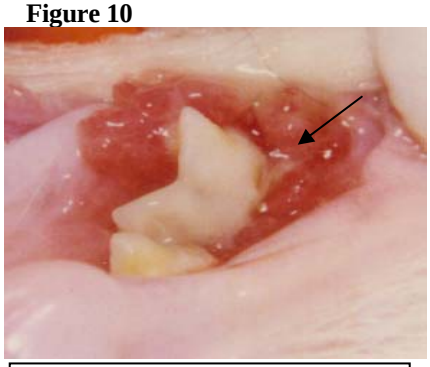
Gingivitis in a 6 month old cat with minimal tartar. This cat had a bacteremia of 1000 *Bartonella*/ml and was Fe*Bart* test +4

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*

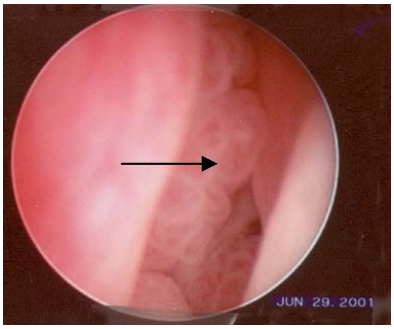
Upper Respiratory Disease	No. Tested	No. Positive	% Positive	Difference
HEALTHY- NO KNOWNRISK FACTORS	840	170	20%	X
URI	4,643	2,188	47%	2.4X
Rhinitis	643	357	56%	2.8X
Sinusitis	230	116	50%	2.5X
Upper Respiratory Disease Totals:	5,516	2,661	48%	2.4X

* 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]

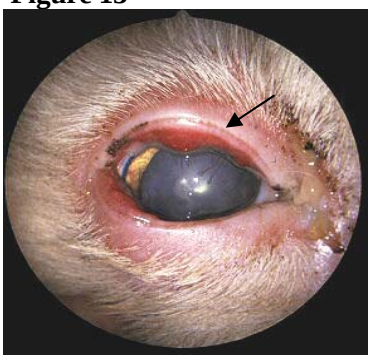
Table 12

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**

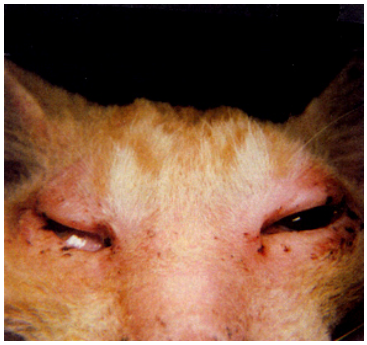
* Totals do not equal total number of cats tested since many cats had multiple inflammatory diseases.

Figure 13



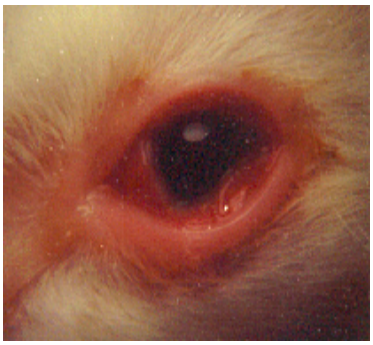
Uveitis & Blepharitis

Figure 14



Conjunctivitis & Blepharitis

Figure 15



Conjunctivitis

Figure 16

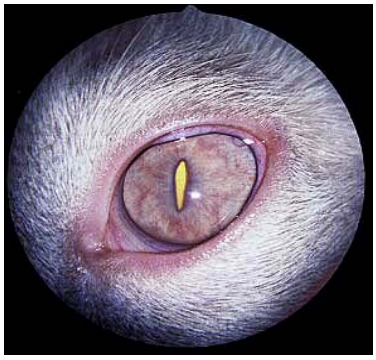


Figure 17

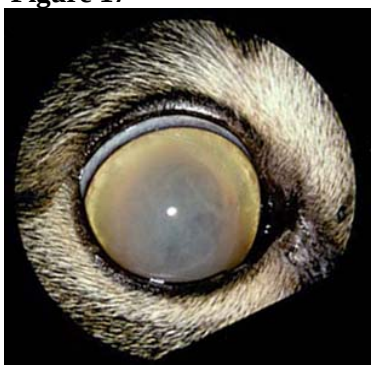
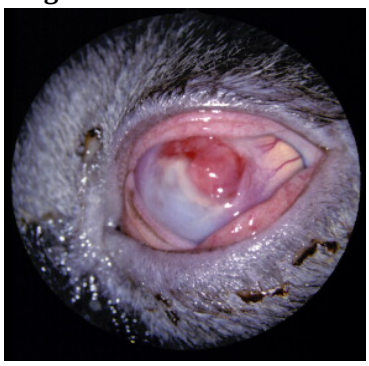


Figure 18



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).

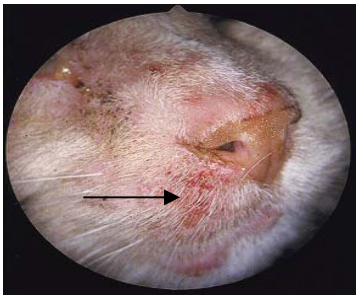


Figure 19
Left: Chronic facial rash (dermatitis) in a cat with chronic uveitis. The uveitis and facial skin rash resolved completely with azithromycin therapy.[11] **Dr. Kerry Ketring: All Animal Eye Clinic, Cincinnati, OH**

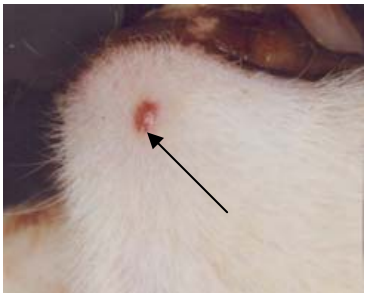


Figure 20
Right: Chronic chin papule "acne" in a young cat who also had gingivitis and chronic URI.

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

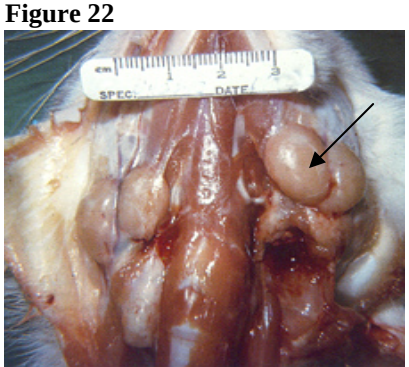


Figure 22
Left: Chronic lymphadenopathy in a stray cat that was Fe*Bart* test +4 and had a bacteremia of 400 *Bartonella* /ml.

Figure 21

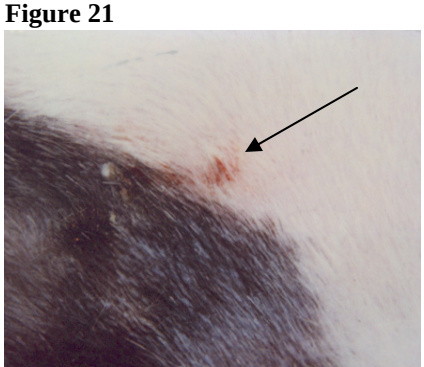


Figure 21

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****

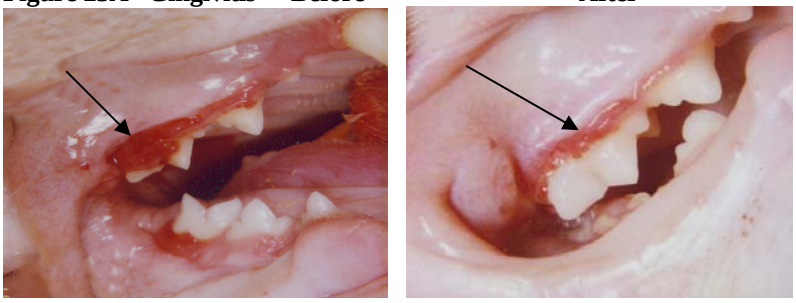
The blood glucose levels of *Bartonella*-infected diabetic cats, who are being maintained on insulin, should be monitored closely during azithromycin therapy. Alteration of the insulin maintenance dose may be required.

Clinical Therapy Results:

Gingivitis:

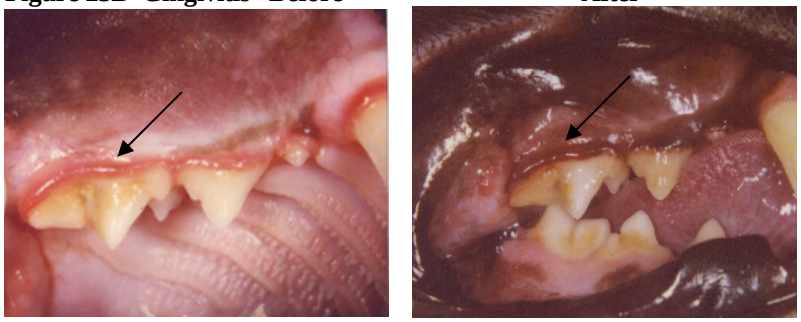
A total of 213 of the 254 (84%) treated cats with oral diseases showed a clinical improvement of 50% or greater.[58,61,63] Clinical improvement was observed in 167 of the 187 cats with gingivitis after azithromycin therapy: excellent response n= 124 (66%); good response n= 34 (18%) and fair response 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**

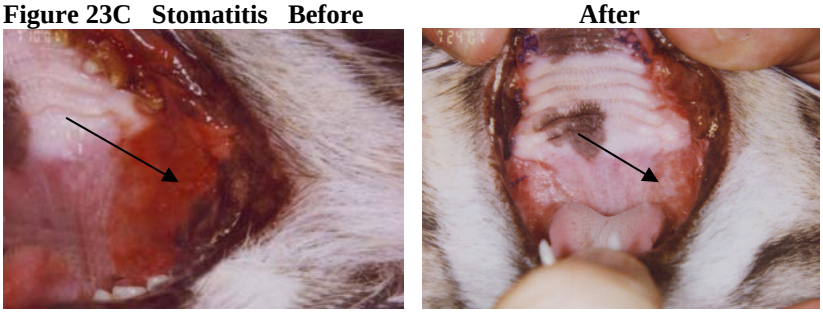


Before:
Gingivitis- 6 month old stray cat with fleas and minimal tartar. Fe*Bart* Test +4 strong positive. 1000 *Bartonella henselae* CFU/ml were isolated from the blood before therapy. Raised erythematous skin nodule also present
After: 2 years after therapy
Gingivitis and skin nodules completely resolved. 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**

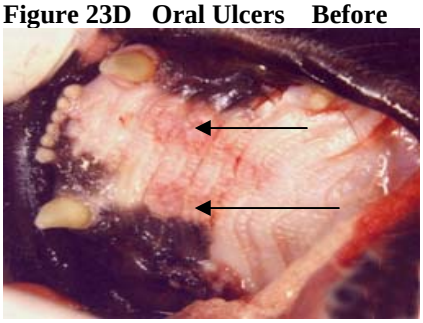


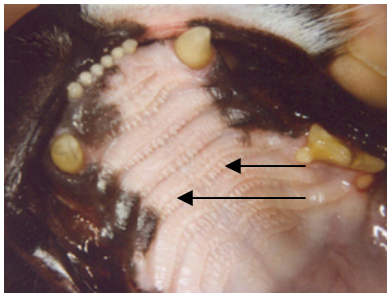
Before:
Stomatitis and gingivitis- 8 year old cat with severe tartar. Fe*Bart* Test +3. Dental prophy with multiple extractions performed and azithromycin therapy given.
After: 2 month after therapy
Stomatitis and gingivitis resolved 80%. By 6 months the stomatitis resolved completely. The *Bartonella*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

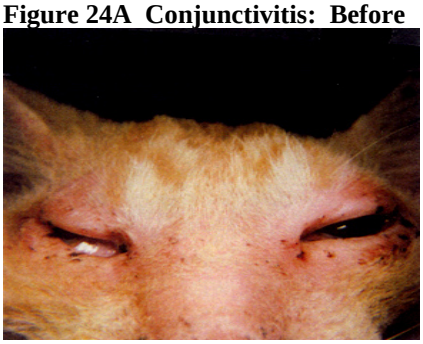
After: 3 month after therapy
Oral Ulcers completely resolved.

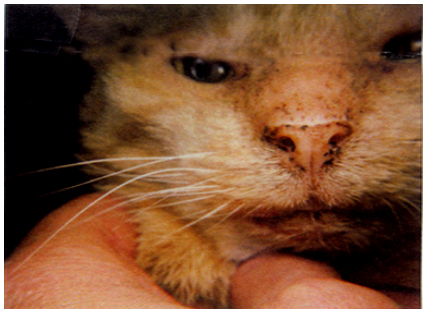
Other Disease:

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:

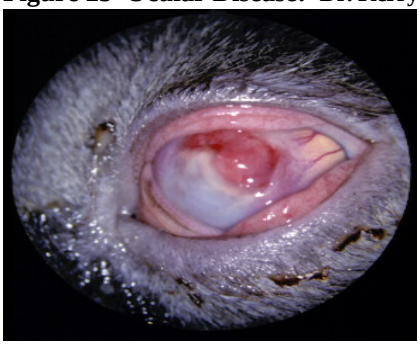
A total of 45 of the 47 (98%) treated cats with upper respiratory infections showed a clinical improvement of 50% or greater. Clinical improvement was observed in 98% of the treated cats: excellent response n= 42 (90%); good response n= 2 (4%); fair response n=2 (4%) whereas 1 cat (2%) did not improve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

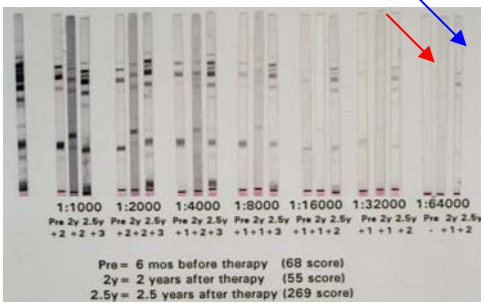
In general, there was a 2 fold or greater decrease in *Bartonella* antibody titers in about 80% of cats treated with azithromycin who clinically improved (Figure 26).[61,63] Some cats, who clinically improved had no decrease in their *Bartonella* antibody titers whereas, some cats, with marked decreases 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.

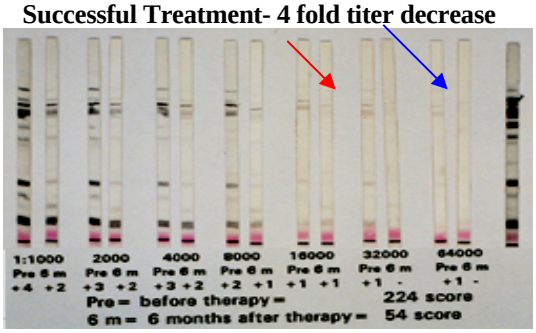
Figure 26 **Western Immunoblot Therapy Titration Tests**

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.

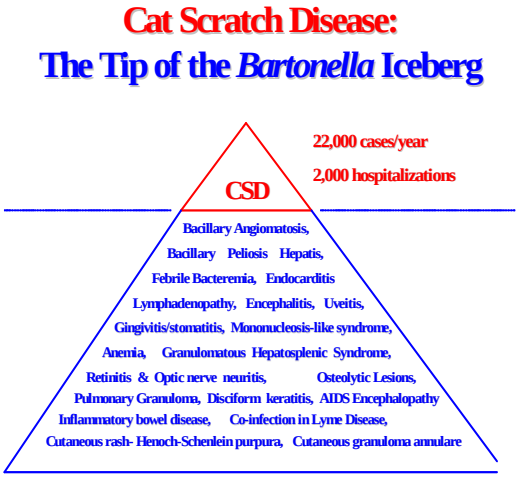
It is interesting to note that, where the diagnosis was indicated, all of the infected dogs had diseases (gingivitis, fevers of unknown origin, lymphadenopathy, uveitis, and endocarditis) that are caused by *Bartonella* in cats and in people. This demonstrates that the pathogenesis of *Bartonella* is 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.

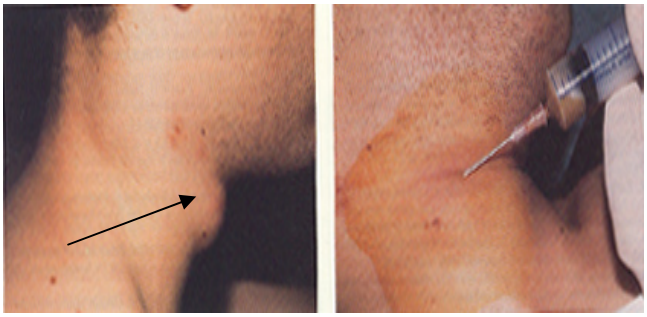


Figure 27
Cat Scratch Disease:
Cervical lymphadenopathy (arrow) in a 17-year-old boy with cat scratch disease who had been scratched by a kitten. Pus was aspirated from the enlarged lymph nodes.
NE J M 340:108, Jan . 14, 1999

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

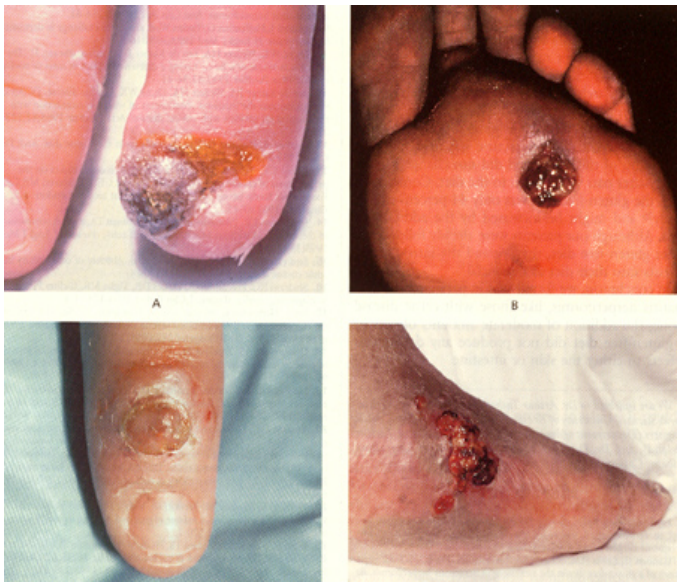
gram-negative bacilli within the vegetations. All cultures of the lesions were sterile. The girl had exposure to birds and kittens and the *B. henselae* titer on day 7 was 1:8192.

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.

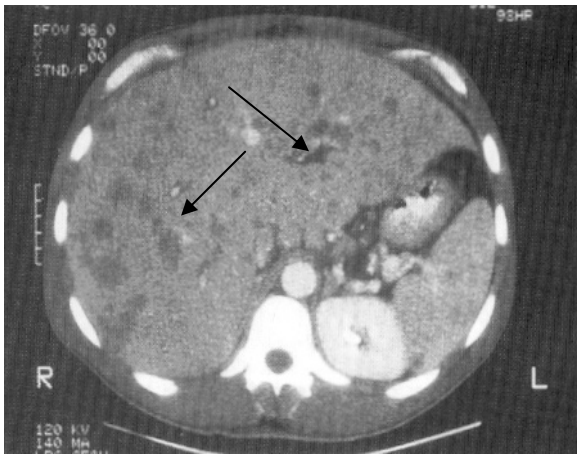
Case 4. A 12-year-old girl was hospitalized after 3 weeks of intermittent fevers (101-105.1° F). There were enlarged and tender inguinal lymph nodes. A colonoscopy showed nodularity with mucosal edema in the terminal ileum. The girl had a recent history of dog and kitten scratches. The *B. henselae*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



<u>Bacillary angiomatosis (BA)</u> (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]

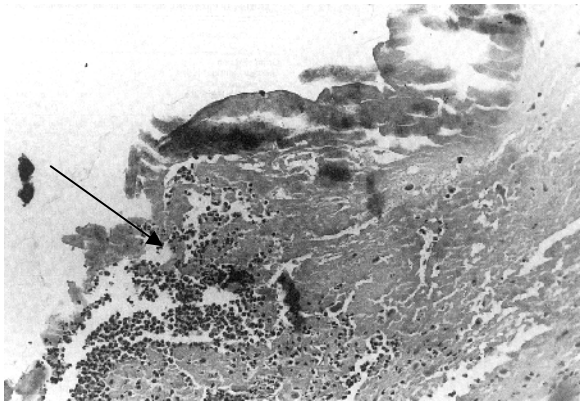

Figure 30 NEJM 345:1321, Nov. 1, 2001

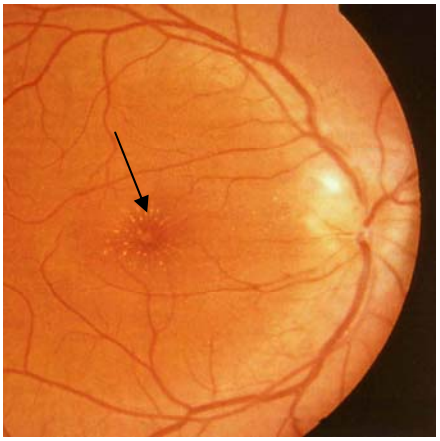

Figure 31
Chorioretinitis caused by *Bartonella henselae*. Bilateral macular papilledema with stellate exudates (arrow) in a boy who lived with a new kitten. NEJM 343: 1459, Nov.16, 2000. There are numerous reports of similar *Bartonella*-induced ocular diseases in cats and

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

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