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NEWSLETTER

Feline *Bartonella*:
Public Health Implications: Lessons Learned From Case Histories

Evelyn E. Zuckerman, Editor **Winter 2006** **Vol. 5, Number 1**

In This Issue:

In the Winter 2006 issue of the NVL Newsletter we will cover the lessons learned from case histories of human *Bartonella* diseases caused by feline *Bartonella*. Feline *Bartonella* pose the greatest threat to human health since cats live in the most intimate relationship to humans than any other *Bartonella* reservoir host animal.

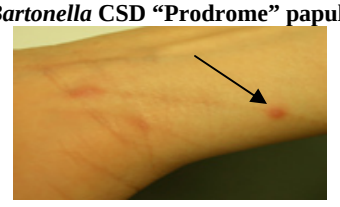
Human *Bartonella* Diseases Occurring in Households with *Bartonella* Infected Cats:

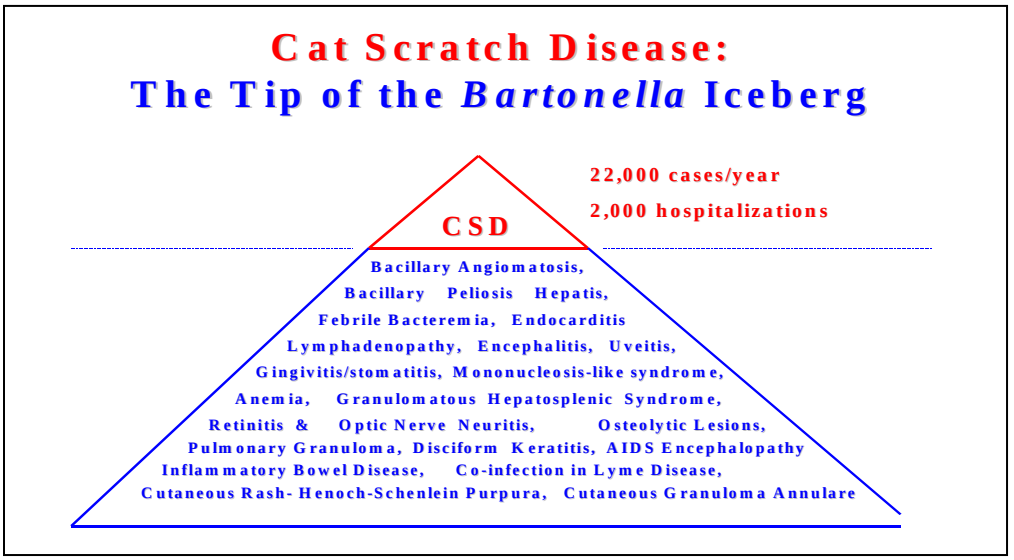
For the past 5 years this laboratory, with the collaboration of many practitioners, has investigated cases of human *Bartonella* diseases in households where we tested cats. As we have previously described in our Newsletters, cat scratch disease (CSD) is only the "tip of the *Bartonella* disease iceberg." Many serious *Bartonella* diseases occur with or without the classical CSD prodrome. The diseases seen below the surface of CSD in the iceberg figure occur far more often that most veterinarians or physicians realize. We have investigated the following cases:

1. Classical CSD "Prodrome" in the Wife of a Veterinarian:

The wife of a veterinarian, who handled many *Bartonella*-infected cats, was scratched by a client's cat. Although she immediately disinfected the wound, several days later a classic papule developed in one of the scratches (see figure below). The veterinarian was very aware of *Bartonella* and was testing most cats seen in the practice. Despite reluctance by her physician, he insisted that his wife be treated with azithromycin for 3 weeks. The lesion resolved in several weeks and no lymphadenopathy or severe disease sequelae occurred. The *Bartonella* antibody titer decreased 8 fold after therapy by our research human titration test. There was no disability and the cost was less than $250 due to the awareness of the human *Bartonella* symptoms.

***Bartonella* CSD "Prodrome" papule**





2. Chronic Fatigue Syndrome with Co-infection with *Borrelia* (Lyme):

A 16-year old boy living in New York State developed a left eyelid droop in September 2004. He lived with an 11-year old *Bartonella* infected DSH cat, obtained years before as a stray. The family's veterinarian never discussed *Bartonella* with the family over the years. Although no fleas were seen on the cat, the family had found ticks on the cat several times. The cat was also serologically positive for *Borrelia burgdorferi*. The boy developed headaches, extreme fatigue, joint pain, conjunctivitis and was doing poorly in school. In January 2005 he developed a painful, enlarged lymph node behind his left ear. He was seen by the following doctors: 1) a pediatrician, 2) a local neuro-ophthalmologist, 3) a neuro-ophthalmologist at Harvard, 4) an infectious disease specialist, 5) a neurologist, 6) a family practitioner and 7) a specialist in tick borne diseases. An initial diagnosis of myasthenia gravis was later discarded. At the urging of the boy's mother, who consulted a Lyme disease support group and did extensive research on the Internet, a *Bartonella* antibody test was performed. The IgG titer was positive at 1:128, but the infectious disease specialist interpreted the result as "borderline," and did not treat with antibiotics.

Over the 6-month duration of the illness the boy was hospitalized for various periods: had an MRI and a CAT scan, blood culture, was treated with several antibiotics, and had a PIC line inserted for 3 weeks of therapy. Finally, the 7th physician, the specialist in tick borne diseases, suggested the diagnosis of atypical *Bartonella* infection (CSD) and the boy was treated with azithromycin for several weeks. The boy slowly made a full recovery. The illness caused disability for 6 months and cost more than $40,000 in medical bills.

3. Which of these cats made a 12-inch wound in the chest of a 50-year-old man?

Answer on back of this page.

Lion

Cougar

?

Cheetah

Miss Kitty, DSH

Answer: Miss Kitty

3. Vegetative Aortic Valvulitis:

Yes, Miss Kitty, a 6-pound, 6 month-old, *Bartonella* infected female DSH stray kitten, caused a 12-inch thoracic wound by a playful scratch months earlier. That scratch transmitted *Bartonella henselae* to a 51-year-old immunocompetent man, which resulted in a clinical syndrome that ended in open-heart surgery (12" thoracic incision) to replace the aortic valve due to *Bartonella henselae*-induced vegetative valvulitis.

It all started when a cute 3-month-old stray was brought into the house after a trip to the veterinarian for worming, vaccinations and flea medication. At that visit, the veterinarian made no mention of the possible public health danger of *Bartonella* from stray kittens, and after this general excellent health assessment, the kitten became a member of the household. Although the kitten was playful, there was no known significant scratch or bite noted. Three months after the kitten came into the household the owner developed persistent fever, headache, general weakness, clubbing of his fingers, severe leg cramps, and night sweats that persisted for weeks. Right axillary lymphadenopathy (CSD prodrome) occurred several weeks later. After examinations by several physicians, the patient was referred to a rheumatologist for the leg cramps. The rheumatologist heard a heart murmur and asked the patient if he owned a cat. The patient was diagnosed with *Bartonella* infection by serology and referred to a cardiologist.

After several cardiac diagnostic tests, a diagnosis of culture-negative aortic valve vegetative valvulitis was made. The patient was referred to a world famous clinic for aortic valve replacement. The removed valve was analyzed and found to contain *Bartonella henselae* in the vegetative lesion. The illness caused 6 months of disability and cost more than $150,000 in medical bills. One wonders what would have happened had the veterinarian recommended *Bartonella* testing at the time of the kitten's first health exam. However, it should be noted that most veterinarians do not discuss the public health aspects of feline *Bartonella* with their clients. *Bartonella*-induced endocarditis and valvulitis is a severe sequelae of the "CSD" syndrome.[1,2]

4. Veterinary Technician- Chronic Fatigue Syndrome:

A veterinarian received a call from a colleague asking if he had a technician available to work in his hospital since his technician was very sick with persistent fever, headaches, and severe fatigue. The technician thought that she had chronic fatigue syndrome. The veterinarian remembered our human *Bartonella* iceberg figure and suggested to his colleague that the sick technician have a *Bartonella* test. She had to convince her physician, but the *Bartonella* test was performed and the result was positive. The technician made a full recovery after appropriate antibiotic therapy. The duration of illness was 6 weeks and cost about $500.

5. Atypical CSD Syndrome in a Child Presenting as Deep Neck Space Infection:

A 4-year old boy, living with 2 adult cats, developed a sore throat, fever of 103° F, and a large swelling on the right side of his face, about 2 inches below his ear. He complained of muscle and joint pain. His illness persisted for 3 weeks and the family's pediatrician referred the child to ENT specialists at a large University Hospital. The boy was hospitalized and quarantined for some time. The swelling was surgically drained, once from the side of the face and twice in the throat near the tonsils. Dye contrast CT scans were performed 3 times. After 5 weeks the child was referred to an infectious disease physician, who diagnosed CSD clinically and performed a *Bartonella* serology, which was positive. The boy was treated with the appropriate antibiotics and made a full recovery. Although there was no history of a cat bite or scratch from the family's pet cats, 1 of the 2 cats tested positive for *Bartonella*. The duration of the illness was 8 weeks and cost the family (insurance) more than $80,000. Deep neck space infections are atypical severe sequelae in 7% of CSD cases.[3]

Lessons From These Case Histories:

1) Physicians do not know much about atypical *Bartonella* diseases in their patients; 2) Those physicians that do know of *Bartonella* diseases feel that treatment need only be given for a few days; 3) Incorrect or delayed diagnosis of a *Bartonella* disease can be life-threatening or result in severe sequelae; 4) *Bartonella* diseases can be financially costly[4]; 5) Most veterinarians DO NOT discuss the public health risks of feline *Bartonella* with their cat owning clients.

Recent *Bartonella* Publications:

CSD Hospitalizations in Children in the United States[4]:

Reynolds and colleagues from the CDC and the Department of Health and Human Service studied the occurrence of CSD in children under 18 years old in 2000[4]. They estimated that 437 cases of CSD in children required hospitalization. Of those children hospitalized for CSD, 24% were atypical presentations with 12% neurologic complications, 7% involvement of organs (liver/spleen), and 5% other presentations. The average hospitalization cost for CSD cases in children was $6,140 and total annual hospitalization charges were approximately $3.5 million. They concluded that childhood cases of CSD requiring hospitalizations did not increase in 2000 compared to previous estimates in the 1980s, despite significant increases in cat ownership in the intervening time.

Bartonella Found in House Dust Mites[5]:

Valerio and colleagues recently reported that house dust mites were infected with *Bartonella* and other Gram-negative bacteria.[5] These Gram-negative bacteria are probably the source of endotoxin that is found in mite allergenic extracts. The *Bartonella* species detected were *B. henselae* (cat & dog), *B. quintana* (human & cat), *B. vinsonii* (dog) and *B. grahamii* (woodland rodents). It is not known if house dust mites transmit *Bartonella* among animals or people.

Bartonella quintana Found in Cats[6]:

La and colleagues have recently found *B. quintana* for the first time in pet cats[6]. Until this observation, *B. quintana* was thought to be a human *Bartonella*, restricted to humans, and to be transmitted only by the human body louse *Pediculus humanus corporis*. *B. quintana* appears to have originated from *B. henselae*, the prototypic feline *Bartonella spp*., through the loss of several important genes. This now expands the known feline *Bartonella* to six species. Of interest, both *B. henselae* and *B. quintana* were found in the dental pulp of cats.

Bartonella Helped to Defeat Napoleon's Army in 1812[7,8]:

The 1812 invasion of Russia by Napoleon is one of the worst military defeats in history. Only about 25,000 of the 500,000 soldiers sent toward Moscow survived. Many of these lice-infested soldiers died of febrile diseases, not in combat. In a fascinating recent article published in The Journal of Infectious Diseases, Dr. Didier Raoult and his colleagues found that roughly 3,000 of Napoleon's solders, found in a mass grave in Vilnius, Lithuania, were killed by lice-borne diseases such as trench fever (*Bartonella quintana*) and typhus.[7] A recent finding concluded that *Bartonella quintana* was derived from the feline *Bartonella*, *Bartonella henselae*, through the loss of 18% of the genome and genomic islands (bacteriophage regions), and thus genome mobility.[8] Remnants of lice found in the mass grave had DNA of *Bartonella*, suggesting that *Bartonella* caused a significant percentage of the deaths of these soldiers.

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NEWSLETTER

The Eyes Have It: *Bartonella* Tropism

Evelyn E. Zuckerman, Editor **Spring 2006** **Vol. 5, Number 2**

In This Issue:

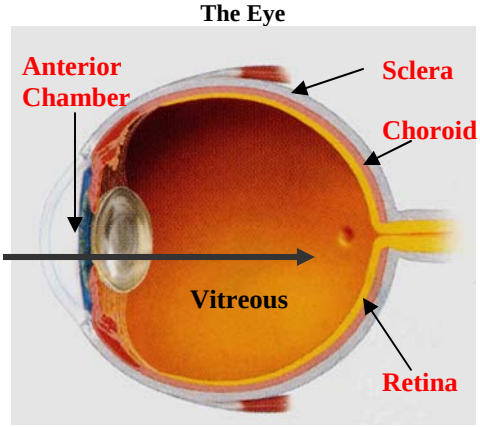
In the Spring 2006 issue of the NVL Newsletter we will discuss one of the most common sites for *Bartonella* infection in cats and humans; the eyes. It appears, possibly due to the vascular architecture of the eyes, that *Bartonella* has a tropism for ocular tissues in cats and humans.

The Eye

Background:

The eye is an anatomical extension of the central nervous system (CNS) and like most cells of the CNS many cell types in the eye cannot regenerate after injury. While inflammation and immune-mediated injury can be tolerated by many tissues that are capable of regeneration, the eye cannot tolerate even mild inflammation without the potential loss of it's main function, vision.[1] Thus, the eye must maintain a clear path for light from outside to traverse through the lens and reach the retina in order for sight to occur. The complex functions of the retina and the connections to the visual cortex would be meaningless if the structures from the cornea, anterior chamber, lens or vitreous were damaged by inflammation blocking the accurate transmission of light.

The Eye



The Eye

Anatomy:

The eye is made up of three coats: 1) Sclera: the outer fibrous protective coat, 2) Choroid: the middle vascular and pigmented coat, and 3) Retina: the inner nervous coat. The vascular nature of the choroid predisposes it to pathological damage. Bacteria and bacterial emboli often lodge in the choroid, and leukocytes can escape the vasculature to invade the choroidal stroma and retina. The retina is often involved in inflammatory processes of the choroid and this process is called chorioretinitis. Some of the infectious agents that cause chorioretinitis are *Bartonella spp*. *Toxoplasma gondii*, *Coccidioides immitis*, *Mycobacterium tuberculosis* and various viruses.

Ocular Immune Privilege:

Niederkorn has described this phenomenon in an excellent review entitled "Ocular Immune Privilege: Nature's Strategy for Preserving Vision."[1] The anterior chamber of the eye permits the survival of foreign tissue and tumor grafts, a phenomenon that was thought to result from sequestration of intraocular antigens from systemic lymphoid tissues of the body. It is now known that immune sequestration is not responsible for this immune privilege, but rather there are an array of local anatomic, physiologic and immunoregulatory factors responsible. The ocular fluids of the anterior chamber, the aqueous humor, possess remarkable immunomodulary factors that suppress or dampen the immune response in order to spare collateral damage to innocent ocular bystander cells that are unable to regenerate.

Bartonella Occurrence in Cats:

As of April 1, 2006 the results of 107,606 cats tested for infection with *Bartonella species* by the western immunoblot are given in Table 1. Cats were tested from all geographic areas of the United States where exposure to fleas and ticks varies greatly. Thus, 38% of healthy cats were positive, whereas when we carefully investigated the risk factors of 860 cats in the northeast, we found only 20% were infected. Thus, we use 20% as the base line infection occurrence to analyze the occurrence of *Bartonella* in inflammatory diseases of the eye.[2]

Table 1 Occurrence of *Bartonella* in Cats from the United States

Status	Number Tested	Number Positive	% Positive
Healthy*	26,413	10,089	38%
1) No RFs**	5,629	1,756	31%
2) With RFs	20,784	8,333	40%
Diseased Cats	78,095	36,864	47%
Not Specified***	3,098	1,396	45%
Totals	107,606	48,349	45%

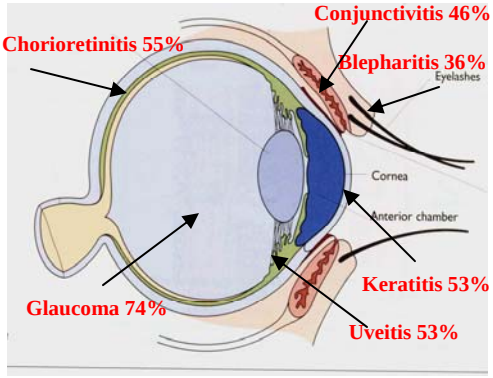
* RFs= risk factors for *Bartonella* infection- flea & tick exposure- hot & humid climates, stray or shelter origin, multi cat household.
** No risk factors reported by veterinarian.
*** No diagnosis given.

Bartonella Diseases of the Eye:

Feline Ocular *Bartonella* Diseases:

Feline *Bartonella* cause inflammatory diseases of all structures of the eye due to their affinity to infect erythrocytes and vascular endothelial cells of all tissues. Since the eye is a highly vascular organ, *Bartonella* are responsible for many ocular diseases that veterinarians diagnose commonly in cats. Dr. Kerry Ketring, All Animal Eye Clinic, Cincinnati, OH, Dr. Craig Fischer and Dr. Melanie Mineo, Animal Eye Clinic of Florida, Clearwater, FL, and our laboratory have reported on the association of *Bartonella* in ocular inflammatory diseases of cats.[3,4] Others have also reported an association of *Bartonella* in ocular disease in cats.[5]

***Bartonella* in Ocular Diseases of Cats**



We detected *Bartonella* in 15,968 ocular inflammatory diseases of cats. Many cats had multiple simultaneous ocular inflammatory diseases such as conjunctivitis and uveitis. A summary of the *Bartonella* status of cats with ocular disease is given in Table 2.

Table 2
***Bartonella* Infected Cats with Ocular Inflammatory Diseases**

Disease	Number Tested	Number Positive	% Positive
Conjunctivitis	12,506	5,791	46%
Uveitis	1,725	911	53%
Corneal Ulcer	687	350	51%
Keratitis	633	328	52%
Chorioretinitis	222	122	55%
Epiphora	81	41	51%
Glaucoma	72	53	74%
Blepharitis	42	15	36%
Totals	15,968	7,611	48%

There are 4 possible interpretations as to the *Bartonella* causation of the ocular inflammatory disease in a *Bartonella* antibody positive cat: 1) *Bartonella* is the sole cause of the disease, 2) *Bartonella* is a partial cause, co-etiologic polymicrobial disease, 3) *Bartonella* is not the cause of the disease but is in the background only, and 4) *Bartonella* has been rejected and the positive antibody test indicates past infection. *Bartonella* are a major threat to the sight of cats and humans due to the chronic nature of the induced ocular inflammation which can eventually overcome the immune privilege of the eye and cause severe damage which the ocular tissues cannot repair by regeneration.

Conjunctivitis:

The most common feline ocular disease is conjunctivitis. Conjunctivitis is an inflammation of the conjunctiva, the mucous membrane covering the anterior surface of the eyeball and the lining of the eye lids. Conjunctivitis can be caused by bacteria, viruses, and fungi. Forty-six percent of 12,506 cats with conjunctivitis were *Bartonella* positive. The following 3 figures show the therapeutic responses of *Bartonella* infected cats with conjunctivitis.

Conjunctivitis: Before and after therapy

Dr. Rene Gandolfi, Castro Valley Companion Animal Hospital, Castro Valley, CA

Uveitis & Conjunctivitis: Before and after therapy

Dr. Kerry Ketring, All Animal Eye Clinic Cincinnati,OH

Uveitis:

Uveitis is inflammation of the entire uveal tract, the iris, ciliary body and the choroids. Uveitis is often a sign of systemic infection. We found 53% of cats with uveitis were *Bartonella* positive.

Uveitis: Before and after therapy

Dr. Kerry Ketring,
All Animal Eye Clinic
Cincinnati, OH

Corneal Ulcer:

The integrity of the eye is threatened by penetrating wounds or perforation by ulceration of the cornea. We found 51% of cats with corneal ulcers were infected with *Bartonella*.

Corneal Ulcer: Before and after therapy

Dr. Kerry Ketring, All Animal Eye Clinic Cincinnati, OH

Blepharitis:

Blepharitis is an inflammation of the eye lids, especially the margins of the lids.

Blepharitis: Before and after therapy

Dr. Jack Broadhurst Cat Health Clinic Pinehurst, NC

Human Ocular *Bartonella* Diseases:

Ocular inflammatory disease occurs in 5-10% of people with cat scratch disease (CSD).[6] The eye becomes involved 1 to 4 weeks after the systemic signs of CSD appear. However, ocular *Bartonella* disease can occur without the recognition of classical CSD syndrome preceding the involvement of the eye.[7] Human *Bartonella* ocular diseases are listed in Table 3

Table 3

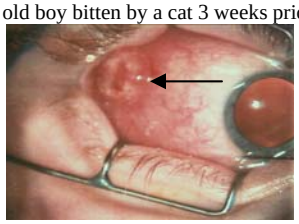
Human *Bartonella* Ocular Diseases
Parinaud's Oculoglandular Syndrome
Uveitis
Chorioretinitis
Conjunctivitis
Disciform Keratitis
Blepharitis
Orbital Granuloma

Parinaud's Oculoglandular Syndrome:

Parinaud's oculoglandular syndrome is the most common human ocular *Bartonella* syndrome. It is characterized by regional lymphadenopathy and mild swelling of the eyelid with a serous to mucopurulent discharge. Severe hyperemia and granulomatous nodules may occur on all conjunctival surfaces (Figure below).

Parinaud's Oculoglandular Syndrome

13 year old boy bitten by a cat 3 weeks prior.



Dr. Kerry Ketring, All Animal Eye Clinic Cincinnati, OH

Conjunctivitis:

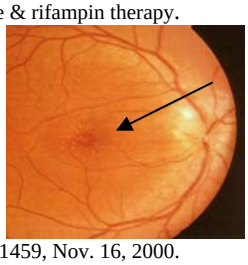
Severe conjunctivitis in a 12 year old girl infected with *Bartonella henselae*.

Dr. Kerry Ketring, All Animal Eye Clinic Cincinnati, OH

Chorioretinitis:

Due to its vascular nature, many infectious agents cause inflammation in the choroid layer resulting in chorioretinitis.[8,9]

Chorioretinitis: Bilateral macular papilledema and stellate exudates (arrow) caused by *Bartonella henselae*. The boy had recently acquired 2 playful kittens. He had transient right cervical lymphadenopathy 2 weeks before blurred vision occurred. His vision returned to normal after doxycycline & rifampin therapy.



NEJM 343:1459, Nov. 16, 2000.

Conclusion:

The eye is a very specialized organ with little ability to regenerate tissue after damage by trauma or infectious processes. Thus, it is important for veterinarians and physicians to be aware of the possible involvement of *Bartonella* in inflammatory processes of the eye in order to prevent permanent damage.

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More *Bartonella* references can be obtained at:
www.nlm.nih.gov/

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NEWSLETTER

Feline *Bartonella* Have Some Nerve!
Neurologic Diseases Caused by Feline *Bartonella*

Evelyn E. Zuckerman, Editor **Summer 2006** **Vol. 5, Number 3**

In This Issue:

The Summer 2006 issue of the NVL Newsletter will review the neurologic diseases caused by feline *Bartonella* in cats and people. Once again we are learning from the human experience with feline *Bartonella*-caused neurologic diseases and thus looking for corollary diseases in cats. We think we have found some!

Neurologic *Bartonella* Diseases of Cats and People:

Introduction:

Once again the occurrence of human diseases of the nervous system, caused by feline *Bartonella*, have given veterinarians clues as to possible corollary diseases in cats, the bacteria's natural reservoir host. There are many publications on human neurologic diseases caused by feline *Bartonella*. We will concentrate on diseases of the central nervous system and exclude retinitis and optic nerve neuritis, which were discussed in the last issue of our Newsletter.

There are 3 possible mechanisms by which any bacterium may damage a tissue: 1) direct effect such as invading cells and causing damage or cell death, 2) secreting a bacterial toxin which causes cell damage, or 3) by inducing inflammation resulting in space-occupying granulomas or by inflaming the vasculature supplying the tissues-vasculitis or arteritis.

Human Neurologic Diseases:

Although most physicians are familiar with the classical Cat Scratch Disease (CSD) where the prodrome is a papule at the scratch or bite site, fever, and regional lymphadenopathy proximal to the papule, many are not familiar with the sequelae or complications that can occur. It has been estimated from the medical literature that sequelae occur in 5% to 13% of CSD patients.[1] The sequelae include skin disease, major organ involvement, ocular disease and neurological diseases. Approximately 2% of the 22,000 annual cases of CSD in the United States develop neurologic complications.[2,3] In one study, 25% of the 36 patients with CSD who were hospitalized had neurologic complications, and the majority experienced lengthy hospital stays.[3] The various neurologic diseases caused by feline *Bartonella* in humans are listed in Table 1.

Table 1

Human Neurologic Diseases Caused by Feline *Bartonella*

Encephalitis
Encephalopathy- Granulomas
AIDS Encephalopathy
Meningitis
Seizures
Status Epilepticus
Coma
Dementia
Aggression- Combativeness
Headaches- Encephalalgia
Hemiparesis

Encephalitis:

Encephalitis, inflammation of the brain, is a common neurological sequelae of CSD (*Bartonella* infection) in people. There are numerous causes of encephalitis: viruses (*Herpes viruses*, Arboviruses, Rabies, and Enteroviruses), bacteria (*Borrelia burgdorferi*, *Bartonella*, rickettsia, and *Mycoplasma pneumoniae*), fungi (*Coccidioides immitis* and *Histoplasma capsulatum*), parasites (Amebae and Helminths), and noninfectious causes (autoimmune diseases, cardiovascular diseases and cancer). However, in many cases (32%-75%) of encephalitis the etiology is unknown.

There are numerous reports of feline *Bartonella* induced encephalitis in people. [2,3,4] Many of the encephalitis patients present with seizures, severe headaches and altered mental status (combativeness, dementia).[4] One recent case of meningitis and encephalitis was fatal in a 4-year-old girl from Tennessee.[5]

In a 2 year study of the etiology of encephalitis, 7 (2%) of 334 cases were caused by feline *Bartonella*.[2] Four of the 7 cases occurred in children 7 years of age or younger.

Encephalopathy:

Encephalopathy, any disease of the brain, is the most common neurologic sequelae of CSD (*Bartonella* infection) in people.[3-8] In the medical literature encephalopathy is usually used to refer to granulomatous lesions of the brain.

A severe case of encephalopathy occurred in a 10-year-old girl who had a 3 week history of pain in the left ear, fever, and malaise.[6] CT and MR imaging showed a mass in the left middle cranial fossa (arrow Figure 1) and liver lesions.

Figure 1

Roebuck, DJ Am J Neuroradiol 19:1294, 1998.

The imaging appearances were consistent with meningioma, lymphoma, or other neoplasms, and a liver biopsy and craniotomy were performed. The craniotomy revealed a granuloma at the left trigeminal nerve. The Warthin-Starry stain of the mass demonstrated *Bartonella* organisms and serology showed a rising IgG titer to 1:1,024 to *Bartonella henselae*. The girl recovered completely after therapy.

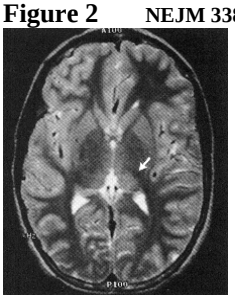
Seizures- Status Epilepticus:

Many of the *Bartonella* infected patients with neurologic complications have seizures and/or status epilepticus. Status epilepticus is defined as repeated seizures or a seizure lasting more than 30 minutes. At one hospital in Virginia, status epilepticus occurred in 6 school children after they recovered from classical CSD. A review of the hospital's records found that 5 of 6 children, with status epilepticus of unknown etiology, were serologically positive for *Bartonella henselae*.[9]

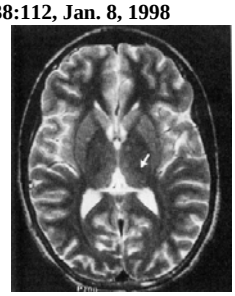
Seizures are likely the result of *Bartonella* granulomas that often localize in the thalamus, which plays an important role in the generation of seizures.[7] An 11-year-old boy living with his parents and 2 kittens was hospitalized unconscious due to seizures.[10] The EMT found the boy confused, combative, and unresponsive to verbal stimuli. He had been well until the day he had the seizures. There was no CSD prodrome and the blood cultures

were sterile. The MRI showed increased signal intensity in the pulvinar of the left thalamus, Figure 2. The boy was IgG positive for *Bartonella henselae* and recovered fully with antibiotic therapy.

Figure 2 **NEJM 338:112, Jan. 8, 1998**



Increased signal intensity in the pulvinar of left thalamus (arrow).



One month after treatment: resolution of abnormal signal

Psychotic Disorders:

The August 2005 issue of National Geographic Magazine had a news item entitled "Who Knew? Your Cat Could Make You Crazy." In the article it reported that some infectious agents, *Toxoplasma gondii* and *Borrelia burgdorferi* can cause psychotic disorders in humans. We feel that *Bartonella* should be added to this list. In this regard, we have studied 2 people who were hospitalized due to psychoses who recovered after therapy for their *Bartonella* infections. Several case histories reported psychotic disorders, dementia, and aggression in people with neurologic disorders caused by feline *Bartonella*.[10, 11]

Feline Neurologic Diseases:

Experimental *Bartonella* Diseases:

Several studies found that experimentally infected cats developed neurologic disease characterized by: aggression, unusual sensitivity to touch and noise, and reduced responsiveness to external stimuli during their infections.[13,14]

Pet Cats:

We have collected data from numerous practitioners who have submitted *Bartonella* tests from cats with neurologic diseases (Table 2).[15]

Table 2 *Bartonella*-Infection in Cats with Neurologic Diseases*

Disease	# Tested	# Infected	%	/X
Healthy no risk factors	840	170	20%	X
Seizures	176	67	38%	1.9X
Aggression	174	71	41%	2.1X
Excessive Grooming	50	26	52%	2.6X
Not Specified	286	120	42%	2.1X
Totals:	686	284	42%	2.1X

* Many cats had multiple signs of neurologic diseases, thus totals in Table exceed the total number of cats tested.

Therapy:

There was clinical improvement of 50% or greater, in 30 of the 38 cats (79%), and complete resolution of disease in 42% of these cats treated for *Bartonella* (Table 3).[16] We have received numerous clinical observations from practitioners that, along with a good clinical response to an inflammatory disease, Azithromycin therapy also improved the "personality" of the cat, making it more sociable with the family. In addition, some aggressive cats became non-aggressive or "mellow" after antibiotic therapy.

Table 3
Therapy of *Bartonella*-Infected Cats with Neurologic Diseases

Clinical Improvement	Number of Cats	%
Unknown	2	5%
None <50%	6	16%
Fair 50-59%	1	3%
Good 60-79%	8	21%
Excellent		
80-99%	5	13%
100%	16	42%
Totals:	38	100%

Dr. Jan White
Renton Veterinary Hospital:

Aggression:

Dr. Jan White, owner of the Renton Veterinary Hospital, Renton, Washington, has been interested in the association of *Bartonella* and aggression in cats. We asked her to give a short summary of her observations:

I (Dr. White) became interested in aggression in cats after reading several studies that found kittens and cats, experimentally infected with *Bartonella henselae*, became aggressive and excitable.[13,14] My own kitten became aggressive in her first year of life, and when tested for *Bartonella* was positive. She was so aggressive that I did not think I would be able to treat her without caging her. However, with each dose of Azithromycin, she became easier to catch and treat. After treatment, she was much easier to handle and was friendlier. As a result of this experience, I began testing aggressive cats for *Bartonella*. In addition, my dog became one of those "biting Cocker Spaniels," tested positive, but has not bitten me since being treated. I have since tested 5 aggressive dogs, 3 of which were positive.

In veterinary practice, there are a significant number of cats that present as "fractious" and are difficult to medicate or even examine. I began to ask owners if their cats had "short tempers" at home or took a whack at people who attempted to pet them. I correlated this information with a history of fleas during or before the time the aggressive behaviors began and started to do *Bartonella* tests based on this information. I have now tested 49 aggressive cats and 27 (55%) were *Bartonella* positive. At the annual exams of these cats following their treatment, I asked about the aggression and owners commonly commented that their cats were friendlier and even more surprisingly, they were thrilled to see that their cats began to play like kittens again, even in cats age 14 and over.

Aggression or just being "plain mean" can be a presenting reason for euthanasia and such behaviors can break the companion animal bond with some owners. A cat in my practice was recently relinquished because "it was never really nice to me and when I acquired a new puppy, it routinely attacked it for no good reason." Our hospital adopted this cat and found it to be *Bartonella* positive. After treatment the aggression improved and we are now looking for a new forever home for this 13 year old cat. It can literally be life-saving to identify *Bartonella* infected aggressive cats/kittens and intervene prior to their being presented for euthanasia. We have seen improvement in the aggression in about 40% of the *Bartonella* infected cats that we have treated. It is important for veterinarians to listen to their clients and think of *Bartonella* when they see fractious cats in the hospital, since human love is not unconditional.

Summary:

***Bartonella* should be considered as a possible etiology for cats with neurologic diseases and aggression.**

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NEWSLETTER

Current Feline Leukemia Virus Research Supports: Confirm All In-Hospital FeLV ELISA Positive Tests by IFA

Evelyn E. Zuckerman, Editor **Fall 2006** **Vol. 5, Number 4**

In This Issue:

The fall 2006 issue of the NVL Newsletter will review feline leukemia virus testing and summarize and interpret new exciting research presented at the recent 8th International Feline Retrovirus Research Symposium: Cat Genomics and Infectious Diseases in the 21st Century held in Washington DC. Dr. Hardy was honored to present the meeting's Banquet Keynote Lecture on October 10, 2006. Of practical importance was the scientific evidence for some of the discrepancies (~32%) between in-hospital ELISA positive FeLV tests and negative confirmatory IFA tests that we have reported.[1,2] These finding indicate that FeLV positive ELISA tests should be confirmed by an IFA test.

The Feline Retrovirus Symposium:

By William D. Hardy, Jr., V.M.D.

The 8th International Feline Retrovirus Research Symposium was expanded to include genomics of the cat and other infectious disease microorganisms such as avian influenza, SARS, feline *coronaviruses*, *Helicobacter spp*., *Bartonella*, and feline retroviruses: FeLV, FIV and Foamy viruses. Dr. Albert Osterhaus gave the Keynote lecture entitled: *Newly Emerging Infections*, Dr. Oswald Jarrett from the University of Glasgow gave a wonderful review of the FeLV field entitled: *How FeLV Changed the World*. My lecture was entitled: *Lessons Learned From Time Spent in Cat Houses: An Historical Overview of the Feline Leukemia Virus and Other Pathogens.* I outlined the biological observations of the discovery of the infectious transmission of FeLV, the development of the first FeLV blood test, the IFA test, and the prevention methods that were developed.[3,4,5,6,7] I also described our findings of the veterinary and public health importance of *Bartonella*. All of our work over the past 37 years was carried out in "cat houses" (households) with the clinical observations of thousands of veterinary practitioners around the country.

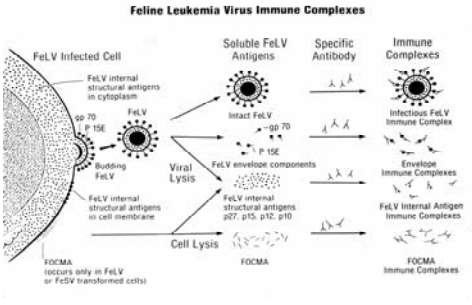
Scientific Explanation for the Discrepancy Between In-Hospital FeLV ELISA Positive Tests and IFA Negative Confirmatory Tests:

Ever since the introduction of the in-hospital FeLV ELISA tests, there have been reports of discrepancies between ELISA positive results and confirmatory IFA tests.[1,2] The problem was significant enough to convene an AVMA Expert Panel on FeLV in 1991 to address the problem.[8] The panel met for 2 days and wrote a recommendation published in the JAVMA which recommended that all FeLV ELISA positive test results be immediately confirmed by an IFA test.[8] The AVMA has not changed these recommendations but the American Association of Feline Practitioners (AAFP) has disregarded the Panel's main recommendation.[9]

An excellent paper presented by Dr. Andrea N. Torres in Dr. Edward Hoover's laboratory at Colorado State University presented evidence that some experimentally FeLV-infected cats will have circulating viral antigens in the blood for long periods after they clear the viral infection.[10,11] These cats tested positive in the in-hospital ELISA test but had no infectious virus in the blood by isolation, were not shedding FeLV in their saliva, and remained healthy. Although IFA tests were not performed, these cats probably represent those pet cats that are ELISA positive but IFA confirmatory test negative. Antigen positive/virus-negative cats should not be managed as if they were infected cats. It has been our recommendation for more that 30 years, that any FeLV test should only detect persistently infected cats that will be shedding virus in their saliva. It is these cats that should be isolated from all other cats in the Test and Removal Program that was developed 30 years ago.[7] It is these cats that the AVMA panel, in their recommendations in 1991, wanted to ensure are the only cats that test positive.

FeLV Antigens:

FeLV tests detect viral antigens in the leukocytes in the blood (IFA Test) or soluble viral antigens (ELISA Tests) released from cells into the blood.



FeLV ELISA Test Positive Confirmation by IFA FeLeuk® Test:

During the past 3 years we have tested 2,821 in-hospital FeLV positive ELISA tests (most were Snap Tests, Idexx) by our IFA test. 32% were not confirmed by our IFA test and should not have been managed as if they were infected.

In Hospital ELISA (+) vs. FeLeuk® IFA Tests

ELISA Positive	# Tests	% Tests
IFA Positive	1,838	65%
IFA % Positive	51	2%
IFA Negative	898	32%
IFA Indeterm.	34	1%
Total:	2,821	100%

During the past 3 years we have also tested 527 in-hospital FeLV negative ELISA tests (most were Snap Tests, IDEXX) by our IFA test. 4.2% were not confirmed by our IFA test and should have been managed as if they were infected.

In Hospital ELISA (-) vs. FeLeuk® IFA Tests

ELISA Negative	# Tests	% Tests
IFA Positive	21	4%
IFA % Positive	1	0.2%
IFA Negative	496	94%
IFA Indeterm.	9	1.8%
Total:	527	100%

The finding of FeLV antigenemia in the absence of FeLV in the blood of some cats makes the recommendation to confirm all ELISA positive in-hospital FeLV tests more imperative.

AVMA FeLV Expert Panel Recommendations:

In 1991 the AVMA Expert FeLV Panel recommended that all FeLV positive ELISA tests **be immediately confirmed by an IFA test**.[8] There is no recommendation to repeat the ELISA test again. ELISA positive but IFA negative results indicate the cat is not infected with FeLV. We now know that most of these cats may be antigenemic but have no infectious FeLV in their blood or saliva and should not be managed as infected cats.

AAFP FeLV Recommendations:

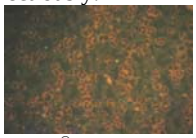
In 2001 (reprinted in 2005) the American Association of Feline Practitioners (AAFP) produced a report on Feline Retrovirus Testing and Management.[9] None of the panel members had any experience developing or evaluating FeLV tests. The AAFP panel did not mention the AVMA FeLV Panel's recommendation, **that all ELISA positive tests should be immediately confirmed by an IFA test**, but rather modified the recommendations. "The work of the AAFP/AFM Advisory panel on Feline Retrovirus Testing and Management was made possible by an educational grant from IDEXX Laboratories, Inc." Editor's note: IDEXX Laboratories is the maker of the predominant in-hospital FeLV ELISA test kit.

The following statements were made:

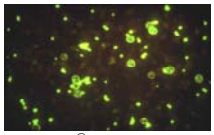
1. "The preferred initial tests are soluble antigen tests, such as ELISA…." Editor's note: The panel never mentioned that the IFA test was used for years as the sole FeLV test and all the biology of FeLV was elucidated using the IFA test.
2. "Indirect immunofluorescent antibody (IFA) tests detect cell-associated antigens." Editor's note: The IFA test detects FeLV antigens in cells that are replicating the virus. They do not mention that the AVMA Expert FeLV Panel recommends the IFA test as the confirmatory test for ELISA positive tests.
3. "In populations with a low prevalence of FeLV infection, more than half of cats for which test results are positive are likely to be uninfected." Editor's note: They neglected to state that the study refers to ELISA tests and not IFA tests. This degree of false positive test results did not occur in studies that used the IFA test.
Editor's note: Although the AAFP report does not recommend that ELISA positive tests be immediately confirmed by an IFA test, they did make recommendations on discrepant test results.
4. "If results of a soluble antigen test are positive and results of an IFA test are negative, both tests should be performed again in 60 days and then annually until results of both tests are in agreement." Editor's note: This is the most unscientific recommendation in the report. There are no scientific publications that show the test results will eventually become concordant. In fact, the recent studies have elucidated the scientific explanation for ELISA positive but IFA negative FeLV test; that some cats can be antigenemic but have no infectious virus in the blood or saliva.

History of FeLV:

FeLV was discovered in 1964 at the University of Glasgow by William Jarrett and his colleagues.[12] In 1968 Helen Laird, Oswald Jarrett and their colleagues reported that FeLV replicates in leukocytes and platelets in the blood.[13] This was a "eureka moment," since I then knew that we could develop an IFA test for detection of FeLV and test cats. In 1973 we developed the test and used it to discover that FeLV was transmitted infectiously.[3,4,5]



FeLeuk® Negative IFA



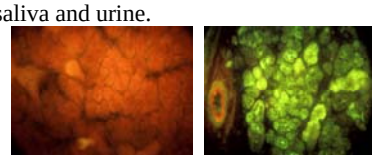
FeLeuk® Positive IFA

Until then, all retroviruses were thought to be transmitted genetically from one generation of animals to the next. Using the IFA test, we and others found that FeLV caused numerous proliferative and degenerative diseases. The degenerative diseases are more common than leukemia and include immunosuppressive diseases and non-regenerative anemia.

Pathogenesis of FeLV Infection:

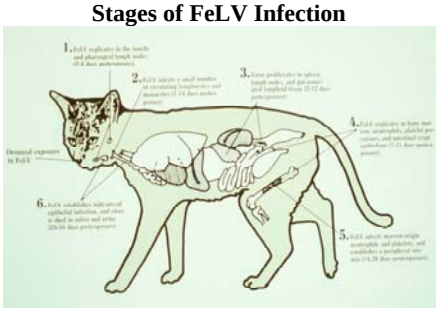
In order to understand the correct use of FeLV tests, it is important to understand the pathogenesis of FeLV infection in cats. The pathogenesis was elucidated by Dr. Jennifer Rojko, Dr. Edward Hoover and colleagues.[14]

After experimental infection of FeLV, which in nature usually occurs most often as oronasal exposure in the head area by mutual grooming, there are 6 stages in the pathogenesis leading to persistent infection. Stage 1: Days- 2-4 FeLV replicates in the tonsils and pharyngeal lymph nodes. Stage 2: Days 1-14 FeLV replicates in a small number of peripheral blood lymphocytes and monocytes. Stage 3: Days 3-12 FeLV replicates in spleen, lymph nodes, and gut associated lymphoid tissues. Stage 4: Days 7-21 FeLV replicates in bone marrow, neutrophils, platelet precursors and intestinal crypt epithelium. Stage 5: Days 14-28 FeLV infects bone marrow neutrophils and megakaryocytes-platelets and establishes a peripheral blood viremia. Stage 6: 28-56 days FeLV establishes epithelial infections in many tissues (nares, oropharynx and salivary glands) and is shed in the saliva and urine.



FeLV negative and positive salivary glands

Stages of FeLV Infection



Courtesy Dr. J. Rojko and Dr. E. Hoover

The long term survival of persistently infected pet cats was poor as 83% died by 3.5 years after we found them positive by the IFA test.[7]

Survival of FeLV Infected Pet Cats

FeLV Status	# Cats	# Cats Died	% Cats Died
Uninfected	512	82	17%
Infected	96	80	83%

Consequences of FeLV Exposure:

Not all pet cats exposed to an FeLV infected cat will become infected. In fact, more exposed cats became immune (42%) to the virus than develop persistent, life-long, infection (30%).

Consequences of Exposure to FeLV

Result of FeLV Exposure	Percent
Persistently infected	30%
Immune to FeLV	42%
Not infected nor immune	28%

It is our contention that the AAFP Panel's report on FeLV testing needs to be immediately revised to reflect the past and current pathogenesis data for FeLV infections. Many owners elect to remove FeLV infected cats from their households and presently do so without understanding that the veterinary profession (AVMA) recommends that all in-hospital positive ELISA tests should be immediately confirmed by an IFA test. 32% of FeLV ELISA positive tests were not confirmed by our IFA test. All in-hospital FeLV ELISA positive tests should be immediately confirmed by an IFA test. ELISA positive but IFA negative discordant cats should be considered FeLV uninfected.

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