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NEWSLETTER

The Controversy Regarding Feline *Bartonella* Pathogenicity in Cats©

Evelyn E. Zuckerman, Editor **Summer 2005** **Vol. 4, Number 3**

In This Issue:

The Summer 2005 issue of the NVL Newsletter will discuss the continuing controversy regarding the pathogenicity of feline *Bartonella* in cats. Several prominent academic feline clinicians on the VIN Message Boards and in their scientific presentations continue to question the ability of feline *Bartonella* to cause disease in pet cats and to fulfill Koch's Postulates. We will explore the scientific facts and misconceptions that exist regarding this controversy.

What are the Criticisms?

1. Feline *Bartonella* do not fulfill Koch's Postulates as the cause of disease in cats, their natural reservoir host.

2. So many healthy cats are infected with *Bartonella* that you cannot determine the disease association in infected cats with inflammatory diseases.

What can we agree on?

1. Most *Bartonella* researchers and academic veterinary clinicians agree that *Bartonella,* derived from cats by zoonotic transmission, cause at least 22 human inflammatory diseases.

2. Canine *Bartonella* cause several similar inflammatory diseases in dogs, their natural reservoir host.

3. The 2 human *Bartonella* (*B. quintana* and *B. bacilliformis*) cause several severe and even fatal diseases in humans, their natural reservoir host.

Let's Examine the Facts!

1. Feline *Bartonella* do not fulfill Koch's Postulates as the cause of disease in cats, their natural reservoir host.

A consideration of Koch's Postulates is necessary to address this criticism. The opening paragraph of an excellent review by Fredericks and Relman in 1996 is most relevant[1]. The co-author David A. Relman was the first to identify *Bartonella* (*Rochalimaea*) in the tissues of a patient with bacillary angiomatosis using DNA methodology.[2]

"Life has changed since the 1880s when Robert Koch elucidated his guidelines, later to be called Koch's postulates, for determining whether a microorganism is the cause of a disease. The horse-drawn buggy bumping over dirt roads has been replaced by the computer-assisted automobile speeding along paved highways. It would be absurd to expect modern cars to abide by traffic rules and standards designed for horse-drawn carriages. Yet, many continue to hold Koch's postulates as the unchanging standard for determining causation in medicine, despite a revolution in biotechnology and leaps in medical knowledge. Recent findings based on the application of new technologies, especially in the fields of microbiology and infectious disease, demand a renewed dialogue on proof of causation and revised guidelines for defining a causal relationship between a microbe and a disease."[1]

The authors continue their analysis of the modifications to Koch's postulates over the last 125 years. "The critical elements of Koch's postulates include a specific association of the microbe with the disease state; scientific concordance of microbiological, pathological, and clinical evidence; isolation of the microbe by culture on lifeless media; and reproduction of disease by inoculation of the cultured organism into a host." These stringent criteria worked well for some bacteria such as *Mycobacterium tuberculosis* but not for others such as *Vibrio cholerae* that caused cholera in some people but can also often be isolated from healthy carriers.

"Furthermore, how does one meet criteria for causation when a pathogenic microbe is also capable of a carrier state (e.g., *Neisseria meningitidis*), causing disease in one individual and not in another? In contrast to the beliefs of Koch and those of his era, we are well aware today that microbial pathogens often cause subclinical infection… Unfortunately, Koch's postulates have frequently been applied to issues of causation with a mathematical zeal that is not warranted in the biological world…. As Alfred Evans noted, failure to fulfill the Henle-Koch postulates does not eliminate a putative microbe from playing a causative role in a disease…. Serological assays offer an independent, but indirect approach to the clinician for diagnosing disease in individual patients and for studying the epidemiology of microbes in host populations."

It is apparent that Koch and his contemporaries were unaware of microbes that had long latent periods and only induced disease in a small number of people or animals that carried the infections. They were unaware of subclinical infections that occur with many viruses and bacteria (e.g., FIV, FeLV, *H. pylori* and *Bartonella* species).

Bartonella have adapted to their reservoir hosts in unique ways. They cause chronic intraerythrocytic infections with as many as 70% of the reservoir hosts, in certain geographical areas, being bacteremic at any one time. The bacteremia is the source of the vector infection (*e.g.*, fleas, ticks and lice). Some authors state that "the *Bartonella* bacteremias, result in few (and if present, very subtle) clinical signs in their specific hosts which contradicts Koch's observation that the blood of healthy humans or animals is free of bacteria."[3] This observation is certainly not true for humans infected with *B. bacilliformis* in Peru where as many as 40-85% of untreated infected people will die, one of the highest mortality rates of all infectious diseases.[4] Nor is it true of dogs infected with *Bartonella* who develop polyarthritis, lymphadenopathy, endocarditis and fever.[5,6] It is also not true for cats experimentally inoculated with *Bartonella* who develop various inflammatory diseases (see Tables below).[7,8,9]

Abnormalities (Diseases) in Cats Experimentally Infected with *Bartonella*

Abnormalities:	Diagnosis/Cats
Lymphadenopathy	13/13
Splenic follicular hyperplasia	9/13
Cholangiohepatitis	9/13
Myocarditis	8/13
Interstitial nephritis	4/13

Kordick, et al. J. Clin. Microbiol. 37:1536, 1999

Abnormalities (Diseases) in Cats Experimentally Infected with *Bartonella*

Abnormalities:	Diagnosis/Cats
Papule at injection site	5/9
Fever	9/9
Lymphadenopathy	9/9
Myositis	3/9
Lethargy	9/9
Neurological signs- aggression	7/9
Anorexia	6/9

Mikolajczyk & O'Reilly Am. J.Vet. Res. 61:375, 2000

In addition, Guptill *et al.* described reproductive disorders in experimentally infected cats.[10] Certainly these experimental studies fulfill the portion of Koch's postulates that requires induction of disease by the inoculation of the suspected pathogenic microorganism. Yet despite these published reports, the critics choose not to accept the data as proof of pathogenicity.

2. High Prevalence of *Bartonella* in Healthy Cats: Frontal and Stealth Attack Strategies in Microbial Pathogenesis.

Merrell and Falkow in a recent review in Nature, one of the 2 most prestigious international scientific journals, discuss pathogenic microbes in military terms of frontal and stealth.[11] One of their 2 examples of stealth agents is *Bartonella*. The authors describe how *Bartonella* and *Helicobacter pylori* evade the adaptive immune responses to establish chronic, if not life-long infection. They discuss the large percentage of animals or humans that are chronically infected with these agents whereas only some develop disease. The Table below summarizes the attack strategies of each class of microorganism and is relevant to our discussion of Koch's postulates and the pathogenesis of *Bartonella* in cats.

Frontal vs. Stealth Pathogenic Bacteria

Frontal- (Aggressive):	Stealth- (Slow-Mild):
Short incubation period	Long/ indeterminate incubation period
Acute clinical sign	Chronic clinical signs
Engages innate immune system	Engages innate immune system
Rapid multiplication	Slow multiplication
Carrier state uncommon	Carrier state common- shedding
Induce sterilizing immunity	Rarely induces sterilizing immunity
Adaptive immune system (IS)	Avoids or manipulates the adaptive IS
Yersinia & Vibrio	*Bartonella & Helicobacter*

Merrell, D.S. & Falkow, S. Nature, 430: 250-256, 2004

When Koch's postulates do not clearly establish the disease etiology of a micoorganism other methods can be used. These include seroepidemiological evidence, pathological evidence, an appropriate animal model, molecular and immunological techniques and therapeutic intervention or vaccine prevention.

Evidence Linking Microorganisms to Infectious Diseases

1. Seroepidemiological
2. Pathological
3. Animal Model (Human Model)
4. Molecular biology and immunology
5. Antibiotic therapy- intervention

1. Seroepidemiological: The combination of the experimental studies previously cited and our seroepidemiological evidence seems overwhelming in support of the association of feline *Bartonella* with inflammatory disease in pet cats.[12] The following Table summarizes our association of *Bartonella* infection with inflammatory diseases in cats.

***Bartonella*-Infection in Cats* with Inflammatory Diseases**

Diseases	No. Tested	No. Infected	% Infected	Difference / X
Healthy: No Risk Factors	840	170	20%	X
Oral Disease	19,823	9,932	50%	2.5X
Resp. Diseases	4,933	2,471	50%	2.5X
Ocular Diseases	3,767	1,820	48%	2.4X
GI Diseases	1,522	747	49%	2.5X
Skin Diseases	399	211	53%	2.7X
Other *Bart.* Diseases	2,534	1,216	48%	2.4X
Total	32,978	16,397	50%	2.5X

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

2. Pathological: The pathology induced by *Bartonella* in all species, human, dog and cats is identical. There is chronic inflammation, granuloma formation and blood vessel proliferation in any tissue due to the tendency of *Bartonella* to adhere to and infect endothelial cells that are present in all tissues.

3. Animal Model: The animal model for feline *Bartonella* pathogenicity is the human. All of the *Bartonella* diseases found in experimentally inoculated kittens and in naturally infected cats were first described in humans. These include inflammatory diseases in all systems: ocular, oral, respiratory, gastrointestinal, musculoskeletal, neurological, skin, and major viscera.

4. Molecular Biology & Immunology: Molecular studies of the mechanism of *Bartonella* disease induction are progressing rapidly and have been reviewed in a previous Newsletter (Vol. 4, No.1, 2005). One of the more interesting observations is the derivation of the human *Bartonella quintana* from the feline *Bartonella henselae* by the loss of gene sequences. *Bartonella quintana* now seems to be restricted to its human reservoir and human louse vector.

5. Therapeutic Intervention: As we have reported at international *Bartonella* meetings and in a previous Newsletter (Vol. 3, No. 4, 2004), we have been successful in eradicating *Bartonella* infection in 84% of treated cats.[13] In addition, the inflammatory diseases in *Bartonella* infected cats were markedly improved or totally resolved in 83% of the treated cats.

Summary: Do feline *Bartonella* Fulfill Koch's Postulates?

A summary of the application of Koch's postulates to feline *Bartonella* and the comparison with those pertaining to *Helicobacter pylori* is listed in the Table below. Most, but not all, are applicable to feline *Bartonella*. The experimental transmission studies and seroepidemiological findings are definitive evidence that feline *Bartonella* induce diseases in their natural reservoir host, the pet cat.

Koch's Postulates for:	*H. Pylori* Peptic Ulcers	*Bartonella* Cat Disease
Microorganism always present in the diseased tissue.	Not always	Not always
Viable microorganisms can be cultivated from the diseased tissue.	Yes, Not always	Yes, Not always
Inoculation of microorganism into susceptible animal reproduces the disease.	Yes	Yes
Microorganism can be detected in the pathological tissue from the diseased animal.	Yes	Yes, Not always

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