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NEWSLETTER

Bartonella: That Gut Feeling

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In This Issue:

The Summer 2016 NVL Newsletter will again review the effects of *Bartonella* in an organ system, the gut- intestinal tracts of animals and humans. The 11th edition of Merriam Webster's Collegiate Dictionary defines "gut" as the bowels, entrails, alimentary canal or the basic visceral or emotional part of a person. *Bartonella* are rare but significant pathogens of the gut. This Newsletter will discuss *Bartonella* disease of a portion of the alimentary tract, i.e. the stomach and small and large intestines only and not the accessory digestive organs, the liver and pancreas, which were covered in our last Newsletter.

The Gut:

The gastrointestinal (GI) tract (Figure 1) consists of the alimentary tract- oral cavity, tongue, esophagus, stomach, small and large intestines, anus, and the microbiome. The accessory digestive organs are the salivary glands, pancreas, liver, and gall bladder.

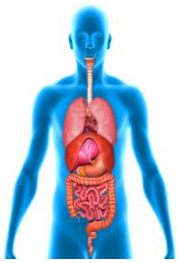


Figure 1

Bartonellosis:

Presently, there are 34 *Bartonella* species of which at least 15 have been shown to cause disease in humans. The most common human pathogenic *Bartonella* species is *Bartonella henselae*, derived from cats, which can cause severe disease in various major organ systems including the heart, brain, eye, lungs, and rarely, in the GI tract. The term cat scratch disease (CSD) is commonly used to include all the pathogenic consequences of *Bartonella* infections. A more precise term is bartonellosis which indicates all the *Bartonella*-induced clinical syndromes in people including the classical CSD and the more severe inflammatory diseases of various organ systems of all animals. The former human *Bartonella* paradigm stated that *Bartonella* caused CSD, a self-limiting condition, occurring mostly in children, characterized by fever, a papule at the scratch site and regional lymphadenopathy. Most cases resolved without antibiotic therapy although there is rare systemic involvement in major organs. In the new paradigm, bartonellosis consists of CSD and more clinically significant pathology in major organ systems.

Gastrointestinal Bartonellosis:

As has been described repeatedly in our Newsletters, feline *Bartonella* infect numerous cell types including erythrocytes, leukocytes, bone marrow cells, vascular endothelial cells of capillaries and parenchymal cells. Thus, all organ systems are susceptible to infection and inflammatory disease as all organs contain capillaries. A relatively rare organ system for *Bartonella* infection, in all animals- cats, dogs and humans, is the GI tract. Humans have had the first and most often reported GI *Bartonella* diseases, probably because they have been more completely investigated.

Human GI *Bartonella* Disease:

In immunocompromised human patients, HIV-infected people, the response is mainly vasoproliferative: Bacillary angiomatosis (BA) refers to primarily skin proliferative vascular lesions that may resemble Kaposi's sarcoma. However, red or brown papules, angiomatous nodules, pedunculated lesions, or deep subcutaneous or granulomatous abdominal organ BA masses also occur.

During the early HIV retrovirus epidemic in the mid 1980s, physicians in many medical centers began to observe life-threatening cases of infections in HIV infected immunocompromised patients.[1] Many of the early AIDS related deaths were due to *Pneumocystis carinii* pneumonia in previously healthy homosexual men. Other secondary diseases were often vascular-granulomatous and even CSD disease, the etiology of which was unknown at the time. It took the AIDS epidemic to identify the secondary *Bartonella* infectious diseases in HIV immunocompromised patients to allow for the isolation of the agent of CSD. By 1990, Relman and his collaborators used PCR-amplified DNA, directly from the BA lesions of an AIDS patient and found that the DNA was closely related to *Bartonella quintana*, the Trench Fever agent of World War I.[2] It was the first microorganism to be identified by DNA technology directly from diseased tissue without having been isolated and grown in a laboratory. Once the etiologic agent was identified, it allowed the epidemiology and zoonotic spread from feline reservoirs to be quickly elucidated. In 1995, one of the earliest *Bartonella* disease publications by Koehler and Cederberg was of a *Bartonella* induced GI disease.[3] By this time we had developed our *Bartonella* western blot test, the Fe*Bart* Test, and were the first laboratory to make *Bartonella* testing available to veterinarians for detection of *Bartonella* infections in cats.[4]

Gastrointestinal hemorrhage: a new manifestation of bacillary angiomatosis.[3] A 24-year-old woman with AIDS presented to the emergency room with upper GI hemorrhage. She had abdominal pain for 1 month and on the day of admission had acute hemorrhage in her vomitus and stool and had fainted twice before arriving at the hospital. She reported having had exposure to several cats 6 months earlier but denied having received any scratches from the cats. A barium study showed abnormal proximal jejunal mucosa with an extraluminal 8.5 X 4 X 6-cm mass. A needle biopsy was performed and the histopathology revealed BA. Warthin-Starry stain found clusters of bacteria in foci of leukocytoclasis. Culture of the biopsy specimen grew *B. quintana*, which at that time had not been found in cats, but has subsequently been isolated from some cats. The patient was treated with 500mg of tetracycline 4 times daily for 3 months with complete resolution of her abdominal mass and hemorrhages.

***Bartonella henselae* and inflammatory bowel disease.**[5]

A 13-year-old boy had fever for 3 weeks, fatigue, anorexia, myalgia, and had lost about 5 pounds. He was given oral amoxicillin followed by cefuroxime without improvement. He showed pain on palpation of the lower right abdominal quadrant. There was increased thickness of the wall of the terminal ileum and enlarged mesenteric lymph nodes on abdominal ultrasound, but the liver and spleen appeared normal. Due to the persistent fever the ultrasound was repeated and now, in addition to the thickened ileum, there were multiple hypoechogenic lesions in the liver and spleen. This finding prompted IFA serologic testing for *Bartonella* and the IgM antibodies were positive and the IgG titer was extremely elevated at 1:8000. The patient then received ciprofloxacin for a week but was switched to azithromycin for 5 days. The fever subsided 2 days after beginning the azithromycin and the ileum and liver and spleen normalized by 6 weeks. This

boy's family did not own a cat but he had contact with a friend's kitten. His friend had been hospitalized a month before for a chronic fever, preauricular lymphadenopathy and non-suppurative conjunctivitis (Parinaud's oculargladular syndrome- one of the earliest described *Bartonella* diseases). The friend's *Bartonella* serology revealed IgM positive and high IgG titer of 1:4096. This kitten transmitted *Bartonella* to 2 children at about the same time. As many studies have indicated, healthy kittens, younger than 1 year-of-age, are the most likely to transmit *Bartonella* to people.[6-7]

***Bartonella henselae* Infection of Prosthetic Aortic Valve Associated with Colitis.[8]**

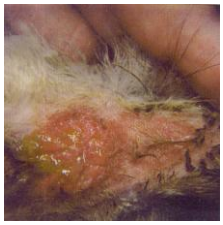
A 61-year-old man with a porcine aortic valve presented with fever, diarrhea, fatigue and intermittent confusion. He was anemic and a colonoscopy revealed chronic colitis consistent with IBD. Blood cultures were sterile and the patient's symptoms continued for 4 months. An infectious disease consultant elicited a history of cat scratches while the patient volunteered at a local animal rescue organization. A repeated echocardiogram revealed prosthetic aortic valve vegetation but blood cultures were again sterile. However IFA serology for *B. henselae* was positive- IgG 1:4096 and IgM 1:1024. After antibiotics failed to improve the patient's condition, the prosthetic valve was surgically removed and real-time PCR was positive for *B. henselae* on the valve. Twelve months of doxycycline and rifampin resulted in clinical improvement. Two consecutive *B. henselae* titers were negative which demonstrated elimination of the infection.

Other Human *Bartonella* GI Cases.[9-14]

There are several other publications of human *Bartonella*-induced "gut" diseases. The first occurred in 1996 in a 60-year-old homosexual man with AIDS.[9] He had no known cat contact but developed bloody diarrhea with multiple colonic BA lesions. Doxycycline therapy for 3 months was curative of the BA. In 2001 a sister and brother developed CSD from contact with a 10 week old kitten they adopted.[10] The 15-year-old girl developed nausea, vomiting and severe abdominal pain. Abdominal CT showed a large mass in the abdomen involving the descending part of the duodenum. The patient and her brother had high antibody titers to *B. henselae*. The patient responded within 3 days of antibiotic therapy. Two cases occurred in 2003, the first in a 38-year-old HIV-positive woman who had massive hematemesis caused by ulcerated BA nodules in the esophagus, stomach, and duodenum.[11] The other 2003 case occurred in a 14-year-old boy with acute abdominal pain and a high fever who had been scratched by a kitten 2 weeks before.[12] A diagnosis of terminal ileitis with high antibody titers to *B. henselae* was made. Azithromycin therapy was curative within 2 weeks. A 2012 case was reported in a 53-year-old women who had been treated for non-Hodgkins lymphoma.[13] She presented with abdominal pain, nausea, vomiting, and weight loss of several months duration. She was the owner of 4 outdoor cats but did not recall any scratch or bite. Clinical workup demonstrated multiple small ulcers throughout the upper and lower GI tract. Doxycycline and rifampin therapy was curative. Finally, the most recent case was reported in 2014 in a 46-year-old woman who presented with abdominal pain and fever.[14] Endoscopy revealed a protruding lesion through the duodenal wall and the *B. henselae* serology was highly elevated for IgM. Azithromycin therapy was curative.

Feline GI *Bartonella* Disease:

During our first 16 years of *Bartonella* testing, a total of 311,307 cats were tested where the submitting veterinarians indicated that 3,441 cats (1.1%) had clinical inflammatory bowel disease (IBD). Table 1 below shows that 43% of these cats were infected with *Bartonella*. Subsequent azithromycin treatment and therapy follow-ups showed that 79% had a clinical improvement of greater that 50% and 32% had total resolution of their IBD (Table 2). A clinical case occurred in a female 4-month-old DSH kitten with severe intractable diarrhea for a month (Figure 2).[15]



Routine antibiotic therapy was ineffective. The Fe*Bart* test was a +4 infected and the kitten completely recovered by day 10 of the 21 day course of azithromycin therapy.

Figure 2 Intractable diarrhea covering the perineum of a 4 month old kitten.

Table 1 Prevalence of *Bartonella* in cats with Inflammatory Bowel Disease

No. Tested	No. Positive	Per Cent
3,441	1461	43%

Table 2 Azithromycin Therapy: Clinical Response of 266 Cats with IBD

% Improved	No. Cats	Per Cent
100%	86	32%
80-99%	63	24%
60-79%	27	10%
50-59%	35	13%
<50%	10	4%
0%	41	15%
Worse	4	2%
Totals	266	100%

Canine GI *Bartonella* Disease:

As of this writing, a search of PubMed shows there have been no published reports of *Bartonella* associated intestinal disease in dogs.

***Gorilla gorilla gorilla* gut: a potential reservoir of zoonotic pathogenic bacteria. [16]**

This fascinating paper, by Didier Raoult's group in Marseille, France found, by real-time PCR of wild Western Lowland Gorilla, *Gorilla gorilla gorilla*, feces from southern Cameroon, Africa, that *Bartonella* spp. comprised 38% of the human pathogenic bacteria in the gorilla gut. Thus, wild gorillas share many of the human bacterial pathogens and may act as a natural reservoir for these zoonotic pathogens.

Summary: Feline *Bartonella* are not benign CSD pathogens any longer, they cause widespread chronic inflammatory bartonellosis in vital organs including the GI tract. Most of these cases were treated with azithromycin, the antibiotic of our choice for the past 16 years.[17]

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***Bartonella* references can be obtained at:**
www.nlm.nih.gov/ or natvetlab.com