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NEWSLETTER

Veterinarian's Roles in 3 Worldwide Zoonotic Diseases:
Bartonella Therapy: the need for long duration and proper dosages

Evelyn E. Zuckerman, Editor **Winter 2023** **Vol. 22, Number 1**

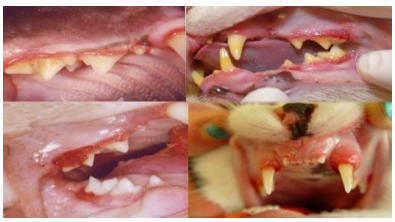
In This Issue:

The Winter 2023 issue of the NVL Newsletter will emphasize the role of veterinarians in dealing with the animal components of three worldwide zoonotic diseases: Bartonellosis, COVID-19, and Avian Influenza (H5N1) and will also review the therapy of *Bartonella* infections and their diseases.

Introduction:

Cat *Bartonella* Diseases- a worldwide endemic:
Bartonella spp. are worldwide and appear to be moderately pathogenic for cats. However, most *Bartonella* infected pet cats show no clinical signs. *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-plasmocytic inflammation. We and others have found that several chronic insidious diseases such as gingivitis, stomatitis and oral ulcers, upper respiratory infections including conjunctivitis, sinusitis and rhinitis, generalized painless lymphadenopathy, persistent fevers, uveitis, keratitis, chorioretinitis, skin diseases, and chronic GI problems such as IBD, have been observed in *Bartonella*-infected pet cats under natural conditions **Figure 1**.

Figure 1
Conjunctivitis **Corneal Ulcer** **Uveitis**



Gingivitis

Stomatitis

Evaluation of *Bartonella* Therapy:

The therapy of *Bartonella* infections have 2 aspects, healthy cats and cats with chronic inflammatory diseases. Approximately 30% of healthy cats in this country are infected with *Bartonella*. Therapy of healthy cats can prevent them from developing a chronic inflammatory disease, but just as importantly, can prevent them from transmitting this stealth zoonotic pathogen to people. Response to therapy by the reduction in *Bartonella* titer after therapy **AND** a significant clinical improvement indicates that *Bartonella* contributed to all, or part of, the inflammation.

Bartonella Therapy:

Bartonella are intra- and extra-cellular bacteria and thus require a long duration of antibiotic therapy.[1-3] When we introduced *Bartonella* testing to veterinarians in November of 1999, we recommended azithromycin, doxycycline and rifampin therapy for cats and dogs based on successful studies done in people. Since then, others have recommended additional antibiotics that are also successful for therapy. Following is a list of recommended antibiotics:

Recommended for *Bartonella* therapy:

Azithromycin- Our first choice 5mg/lb SID for 21 to 36 days.

Doxycycline- Our second choice 5 mg/lb BID for 6 weeks (42 days).

Rifampin- 5mg/lb SID for 21 days. Our choice for re-treatment after initial therapy failure with azithromycin or doxycycline.

Pradofloxacin (Veraflox)- 2.5 mg/lb BID for 6 weeks (42 days).

Combo: Of Doxycycline & Pradofloxacin (Veraflox)-2.5 mg/lb BID 6 weeks (42 days).

Not recommended for *Bartonella* therapy:

Baytril- Enrofloxacin

Convenia-

Orbax= Orbifloxacin- not bactericidal for *Bartonella*.

Noncompliance:

We continue to notice that some veterinarians have used the antibiotics that we recommend, but not for the recommended length of time or daily frequencies that we suggest. For example, we recommend azithromycin as our first choice, given SID for at least 21 days, longer is certainly acceptable. However, some practitioners have only given azithromycin for 5-10 days which we feel is an inadequate duration. In addition, some have given doxycycline SID rather than BID as recommended and some have given it for only 10 to 21 days rather than our recommended duration for 6 weeks (42 days). So **PLEASE** be sure to adhere to our dose and duration recommendations and **PLEASE** indicate the length of your therapy on our submission forms, in the Therapy Titration area.

More problematic is, after the failure of the initial therapy regime, when we recommend rifampin for the re-treatment antibiotic, too many veterinarians are repeating the use of the first antibiotic- i.e., azithromycin after azithromycin or doxycycline after the doxycycline initial therapy failures. We fear the generation and selection of antibiotic resistant strains of *Bartonella* may occur. **We strongly recommend against repeating the use of the same antibiotic that failed in the first therapy protocol.**

Figure 2

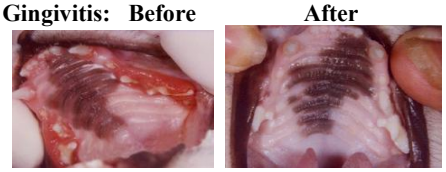
Bartonella Therapy Clinical Results:

URI: Before **After**

Uveitis: Before **After**

Conjunctivitis: Before **After**

Gingivitis: Before **After**



Stomatitis: Before **After**

Evaluation of *Bartonella* Therapy:

There are 1 or 2 parameters for evaluating therapy for *Bartonella* infected cats based on the health status of the cat. 1) For healthy cats, the only parameter to evaluate is the successful elimination of the infection, by the Therapy Titration Test, as there are no clinical signs to evaluate. 2) For infected cats, with inflammatory lesions such as uveitis, gingivitis etc., the 2 evaluation parameters are elimination of infection **and** evaluation of the clinical improvement, if any (**Figure 2**). Our comparative Therapy Titration Test compares the titer of antibodies in the original pre-therapy sample with the post-therapy sample taken **6 MONTHS OR LONGER AFTER THE END OF THERAPY**. Therapy is successful in eliminating *Bartonella* infection if there is a 4-fold or greater titer decrease. It is necessary to wait 6 months from the end of therapy in order to allow the antibody levels to drop (catabolism) after removal of the *Bartonella* antigenic stimulation. Those cats that fail the initial therapy should be retreated with a different antibiotic.

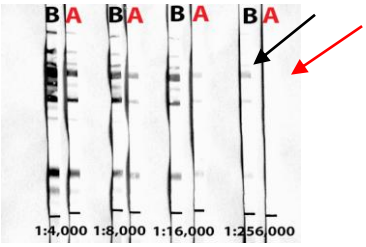


Figure 3. Titration test showing a 16-fold antibody titer reduction (1:256,000 before to 1:1;16000 after) indicating elimination of *Bartonella* infection. B before therapy, **A** after therapy.

Public Health Consideration:

Be sure to caution owners of *Bartonella*-infected cats to avoid being scratched or bitten by their cats during treatment. Immunosuppressed people- chemotherapy, transplant or HIV-infected people should not treat their *Bartonella*-infected cats, someone else in the household should treat the cats.

COMMENT: PLEASE follow our antibiotic recommendations regarding the dosage, frequency of administration (BID vs SID) and duration of therapy 21 days, 42 days etc. In addition, it is important to select a different recommended antibiotic for retreatment of cats who fail to eliminate their infections after the first course of therapy.

The COVID-19 Pandemic: 3+ Years

Statistics: Currently, more than 3 years after COVID-19 was declared a pandemic, the world is in a better place with vaccines and therapy.

*COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU)

COVID-19 Global Statistics*
2/10/2022 and 2/5/2023

Country	Cases	Deaths
World	404,161,627 671,697,951	5,780,644 6,844,517
USA	77,268,991 102,592,195	912,260 1,111,495
China	122,573 4,903,507	4,851 100,922

America has had the most cases (**19.1% 2022** and **15.3% 2023**) and deaths (**15.8% 2022** and **16.2% 2023**). China abolished it's zero COVID policy in 2022 and subsequently has experienced a major COVID-19 outbreak. Add to this, many thousands of pets and wild animals infected from humans (**reverse zoonosis**). These data unfortunately reveal that the world is not over with the COVID-19 pandemic and here in the USA, during the past 28 days, we had an average of 559 deaths each day from COVID-19, data which many experts feel is markedly under-reported. However, the world has given 13 billion, 571 million vaccinations to date and we now have several medications available.

As if all this information where not depressing enough, a new SARS-CoV-2 subvariant CH.1.1, known as "Orthrus," named after a 2-headed dog from Greek mythology that was killed by the hero Heracles (too much information!) is spreading worldwide and accounts for ~20% of variants in this country at present. A preprint paper from Ohio State University researchers reports the CH.1.1 subvariant's ability to evade neutralizing antibodies is "extraordinary." They found that it is highly resistant to both the monovalent and bivalent mRNA COVID-19 SARS-CoV-2 vaccines as well as natural antibodies from people recovered from infections with the BA.4 and BA.5 omicron variants.[8]

The Next Zoonotic Pandemic May Already be Here- Avian Flu H5N1:

Influenza pandemics Except for smallpox, most pandemics are caused by newly evolved viruses. Influenza pandemics have occurred worldwide for centuries and are related to farming birds and pigs. The Spanish flu, also known as the 1918 influenza, was an unusually deadly influenza pandemic caused by the H1N1 influenza A virus. It lasted from February 1918 to April 1920, and infected 500 million people, about a third of the world's population at the time. The death toll is estimated to have been between 20 million and 50 million people, 5-10% of the world's population at that time.[4]

The World Organization for Animal Health (WOAH) has recorded almost 42 million individual cases of avian influenza (bird flu) in domestic and wild birds since the outbreak began in October 2021. Almost 58 million domestic birds, including poultry, have died from the disease, and more than 193 million more have been culled.[5]

Chicken Farm

Biosafety for Bird Flu

Migrating birds on beaches dead from bird flu are handled with biosafety precautions.

Presently, avian influenza H5N1 has decimated chicken flocks worldwide causing the culling of millions of birds. It has spread to numerous wild bird species and now even to some mammals. Since the receptors of the upper airways of birds are less common to those in mammal's, the present H5N1 spares most mammals. Other non-bird species infected with H5N1 are bobcats, red foxes, skunks, raccoons, black bears, otters, and seals.

Mink farm

On a mink farm in Spain, there appears to have been mink to mink transmission of the virus which is very unusual in mammals, and may serve to generate variants that will be more infectious for people. More than 50,000 minks were killed at this facility.[6,7]

Many of the non-bird species probably were infected by scavenging on the carcasses of H5N1-infected wild birds. The World Health Organization (WHO) says 870 humans have been infected with avian flu over the past 20 years, and 457 have died (**53%**). During this current outbreak, there have been a few poultry workers infected by this virus, but fortunately just a few have died. Only the inability for infected people to spread the virus has prevented a pandemic so far. Of course, the fear is that mutants will occur which may make it more transmissible to people and begin a pandemic which may be much more deadly than COVID-19. By comparison, only about 1% of SARS-CoV-2 infected people worldwide have died, a much lower lethality than for former bird influenza pandemics.

The good news is this H5N1 variant seems less pathogenic than earlier versions, we have effective vaccines for poultry and people and also have effective medications. Now we need effective surveillance and planning to prevent another catastrophic avian influenza pandemic.

Summary: Veterinarians are dealing with the animal components of 3 worldwide zoonoses, Bartonellosis, COVID-19, and Avian Influenza. We must stay current and effective in our One Health responsibilities.

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