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GOLDEN RETRIEVER Update

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THE LINK BETWEEN HEMANGIOSARCOMA & BARTONELLA

Vector-Borne Illness May Contribute to Cancer

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TOP CANCER IN GOLDEN RETRIEVERS

MAY BE LINKED TO VECTOR-BORNE *BARTONELLA* PATHOGEN

The discovery of a potential link between the stealth bacterial pathogen *Bartonella* and hemangiosarcoma (HSA) is casting new light on the top cancer concern in Golden Retrievers. A vaccine to protect dogs against *Bartonella*

infection could be key to decreasing the incidence of this highly malignant cancer.

"*Bartonella* may be the most important bacteria that most of the world has never heard of," says Edward B. Breitschwerdt, DVM, DACVIM, the Melanie S. Steele Distinguished Professor of Medicine and Infectious Diseases and co-director of the Vector Borne Disease Diagnostic Laboratory at North Carolina State University, where the discovery was made after 30 years of *Bartonella* investigations.

The vector-borne pathogen *Bartonella* invades and thrives in many different cells of the body. It hides inside the cells of blood vessel walls, where it eludes the immune system, possibly triggering an infectious state that leads to HSA. Its status as a stealth pathogen stems from its ability to go undetected in blood smear tests. Polymerase chain reaction (PCR) is used to amplify *Bartonella* DNA and identify infection.

"Bartonellosis is one of the most important emerging infectious diseases in humans and dogs," Dr. Breitschwerdt says. "Persistent infection or inflammation caused by pathogens can increase the risk of cancer later in life. We suspect pathogenic bacteria, such as *Bartonella*, play a role in different cancers."

"If we could prevent a bacterial infection that can cause cancers such as hemangiosarcoma, it would



be phenomenal,” says Ann Hubbs, DVM, PhD, chair of the Golden Retriever Club of America Health & Genetics Committee.

Similar to *Bartonella*, HSA is stealthy, often going undetected as it develops silently and painlessly. This cancer usually originates in bone marrow. Like *Bartonella*, HSA settles in the thin layer of cells lining the interior of blood vessels. Tumor cells take hold and grow in a vascular web that may contain *Bartonella* infection. These HSA cells have access to the blood supply, which allows them to metastasize to virtually any organ in the body.

About 50 percent of HSA cancer cases occur in the spleen, an organ responsible for eliminating vector-borne pathogens such as *Bartonella* from the circulatory system. Although cardiac HSA is less common, it is the most common heart tumor in dogs. Importantly, *Bartonella* DNA has been amplified from both cardiac and splenic HSA, indicating that the spleen is not preferentially removing the bacteria from the bloodstream. Less frequently, HSA occurs in sites such as the liver, lungs, kidneys, and skin. HSA of the skin is typically less aggressive than HSA in the spleen or heart.

Bartonellosis affects three organ systems, sometimes causing illness in more than one system. Cardiovascular cases include endocarditis, inflammation of the inner lining of the heart chambers and valves, and myocarditis, inflammation of the heart muscle. Neurological effects may cause seizures or paralysis, and rheumatologic signs occur in the joints and surrounding tendinous structures. Because the bacteria are able to invade and live in many different cells of the body, this complicates research directed at understanding the disease process.

CLINICAL SIGNS OF BARTONELLOSIS

- Fever
- Diarrhea
- Lameness
- Coughing
- Swollen or inflamed lymph nodes
- Seizures
- Vomiting

Most dogs with HSA have an advanced form of the cancer when it is discovered. Tumor masses cause few signs other than recurring lethargy and pale mucous membranes due to anemia from small bleeds. When HSA ruptures, a dog collapses with internal bleeding, requiring emergency splenectomy. Dogs often die before treatment can begin. Standard of care treatment involves surgical removal of the tumor, depending on the location, and/or chemotherapy. Although treatment is meant to prevent fatal blood loss and extend life, it is seldom curative as tumor metastasis has often occurred.

With one in five Golden Retrievers dying from HSA, the Golden Retriever Foundation is a dedicated champion sponsor of the AKC Canine Health Foundation's [Hemangiosarcoma Research Initiative](#). Since 1995, the Initiative has provided funding of \$3.8 million for 27 research studies.

[A study currently underway in Dr. Breitschwerdt's laboratory at North Carolina State University is seeking to learn about the prevalence of *Bartonella* infection in dogs with splenic and cardiac HSA in different geographical locations of the U.S.](#) This study builds on an earlier one in which the research team found a high prevalence of *Bartonella* infection in dogs from North Carolina with splenic HSA. [These findings were published in](#)

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[the *Journal of Veterinary Internal Medicine* in 2011.](#)

Although the *Bartonella* pathogen has existed and evolved for millions of years, only two species, *Bartonella bacilliformis* and *Bartonella quintana*, were identified worldwide before 1990. More than 44 *Bartonella* species and subspecies are recognized today. Among the most well-known, *Bartonella henselae* causes cat scratch fever.

In 1993, the first incidence of *Bartonella* infection in a dog was identified in Dr. Breitschwerdt's laboratory. “Tumbleweed,” a 3-year-old female yellow Labrador Retriever, had been unsuccessfully treated for nine months when she arrived at the North Carolina State Veterinary Hospital extremely ill with endocarditis.

The infectious diseases team isolated the bacterium, a new *Bartonella* subspecies, which they named in collaboration with researchers at the Centers for Disease Control and Prevention as

Bartonella vinsonii subsp. *berkhoffii*. The risk factors fit Tumbleweed's lifestyle: heavy flea and tick exposure and a rural home environment. Additionally, endocarditis associated with *B. venonii* subsp. *berkhoffii* occurs in large-breed dogs, such as retrievers, having a predisposition for aortic valve disease.

“I wanted to know how often we had missed the diagnosis of bartonellosis in the past,” Dr. Breitschwerdt says. “*Bartonella* species are probably transmitted by more vectors than any other pathogenic organisms that exist on the planet. Primarily vectors such as fleas, ticks, sand flies, and lice carry the pathogen, though spiders, bed bugs, and deer keds (deer flies) can carry these bacteria as well.”

[An early report based on the current study was published in *PLOS ONE* in January 2020.](#)

Using PCR analysis, the research team looked for *Bartonella*, *Babesia* parasites and *Hemotropic Mycoplasma* bacteria in 110 dogs

HEMANGIOSARCOMA RESEARCH INITIATIVE

In 2018, the AKC Canine Health Foundation launched the Hemangiosarcoma Research Initiative to learn more about this aggressive, common cancer in dogs. A longtime supporter of hemangiosarcoma research, the Foundation has provided \$3.8 million in funding since 1985 to support 27 grants that study this disease. These studies have advanced understanding about causes, new treatments and early diagnostics.

with HSA. Samples included fresh frozen HSA tissue, fresh frozen non-tumor tissue, and whole blood and serum banked at the Canine Comparative Oncology and Genomics Consortium. The samples were from 13 Golden Retrievers, 18 Labrador Retrievers, six German Shepherd Dogs, four Bichon Frisé, four Boxers, 34 other breeds, and 31 mixed-breed dogs.

“While 73 percent of all tissue samples from these dogs were positive for *Bartonella* DNA, none of the blood samples were, which indicates that whole blood samples do not reflect the presence of this pathogen,” explains Dr. Breitschwerdt. “The presence of *Bartonella* DNA in 57 percent of cardiac HSA tumors and in 93 percent of non-tumor cardiac tissue is an important finding. Why was *Bartonella* in cardiac tissue when the heart has no role filtering bacteria out of the circulation as does the spleen?”

Knowing that *Bartonella* species, *B. henselae* specifically, is well-established as a promoter of tumor cell proliferation and chronic inflammation, the team speculated that *B. henselae* is a likely cause or cofactor in the development of HSA in dogs. “Because dogs with HSA have increased amounts of plasma VEGF (vascular endothelial growth factor) compared to healthy dogs and because VEGF is present in tumors, this implicates *B. henselae* as a possible cause of HSA,” he says. “In laboratory cultures, we’ve seen

how *B. henselae* induces angiogenesis (the formation of new blood vessels from existing blood vessels) and proliferation of endothelial cells by stimulating the production of VEGF.”

ONE DAY BETTER OUTCOMES

In 40 years as a breeder and owner of Golden Retrievers, Dr. Hubbs has lost a few beloved dogs to HSA. When her son, Adam, struggled because he was blind, deaf and developmentally challenged, nothing could rouse him to interact with the world around him until “Gala” (Tangleburr’s Street Dance CD) came to the rescue.

“Day after day, Gala sat next to Adam, and sometimes she nudged him with her paw until finally he reached out to her,” she says. “He was 3 years old when she taught him to interact with others and changed his life.”

One day shortly before Gala was to compete in her first Open obedience trial, the 9-year-old female collapsed. Despite efforts to save her, treatment proved futile due to extensive heart involvement, and Gala was euthanized later that day.

A couple of years later, Gala’s granddaughter, “Rem” (Paradocs Only In A Dream CDX AX AXJ), became Adam’s best friend, playing a critical role in his life during elementary school. Then, when Rem was 10 years old, she, too, died of hemangiosarcoma.

“It’s these kinds of tragedies, when dogs are such special members of

Purina and the AKC Canine Health Foundation have worked together since 1997 to support canine health research to benefit all dogs.



Picking up where her granddam Gala left off, “Rem” (Paradocs Only In A Dream CDX AX AXJ) became best friends with Adam Hubbs, offering support and comfort. Rem died of hemangiosarcoma at age 10.



Dr. Ann Hubbs shows “Gala” (Tangleburr’s Street Dance CD) at an obedience trial in 2000. One year later, the beloved female died of hemangiosarcoma at 9 years of age.



your family, that motivate people to bring an end to this horrible disease,” Dr. Hubbs says. “It is encouraging to see this research that shows a possible connection between *Bartonella* and hemangiosarcoma. This could one day result in better outcomes for affected dogs.”

Dogs diagnosed early with bartonellosis and treated with antibiotics typically fully recover. “Most dogs require more than one antibiotic that is given over six weeks,” Dr. Breitschwerdt says. “Treatment can be complicated, and a dog can be sick for months prior to diagnosis.”

Dr. Breitschwerdt worries about the zoonotic effect of *Bartonella* on people. “Owners of infected dogs, veterinarians and veterinary technicians are particularly at risk of getting sick,” he says. “I estimate that up to 25 percent of sick veterinarians have *Bartonella* DNA in

their blood due to exposure with infected animals. Direct contact with body fluids, a needle stick, scratch, or bite from an infected animal puts a person at risk.”

Concerns about the effect of *Bartonella* in dogs and the potential link to hemangiosarcoma is also disconcerting. “In our experience, Golden Retrievers may not handle *Bartonella* well, though bartonellosis occurs in all breeds, particularly affecting large-breed and mixed-breed dogs,” Dr. Breitschwerdt says.

Given the predisposition of Golden Retrievers to HSA and the toll of this cancer in the breed, urgency is warranted for research efforts to learn more about *Bartonella* and the chronic inflammation and tissue damage it causes. The North Carolina State University infectious diseases research team currently is analyzing tissue samples from 900 dogs diagnosed with HSA from the Animal Medical Center in New York City, University of

FLEA & TICK PREVENTION CAN HELP PROTECT DOGS AGAINST BARTONELLOSIS

Efforts are underway at North Carolina State University to develop a vaccine to protect dogs from the pathogenic *Bartonella* bacteria. Until then, the best protection for dogs is practicing regular flea and tick prevention to ward off these common vectors that may carry *Bartonella*.

“Minimizing or eliminating flea and tick exposure is more important today than ever before,” says Dr. Edward B. Breitschwerdt of the Emerging and Infectious Diseases research program at North Carolina State University.

A plethora of preventive products is available, including coat sprays, shampoos, powders, combs, collars, natural and holistic choices, and house/yard treatments. “The safety of these products for mammals is very strong,” says Dr. Breitschwerdt. “The active ingredients target the nervous system of insects and arthropods, which differ greatly from those of dogs and humans.”

Dr. Breitschwerdt recommends consulting your veterinarian to determine the best flea and tick preventive for your dog. “Your veterinarian will know which products are safe for breeding dogs, as well as which products are best for a particular geographical area,” he says, noting that year-round prevention is recommended.

Here are the types of flea and tick preventives available:

- **Spot-On Preventives:** A liquid application, spot-on preventives are applied to a dog’s skin at specific areas to spread out via skin oils in a thin layer over the dog’s whole-body skin surface. Periodic applications, usually monthly, are required. These products vary in their water-resistant properties.
- **Oral Preventives:** Given as a chew or tablet at various intervals depending on the product, oral preventives are absorbed into a dog’s bloodstream, quickly settling into the fatty tissues under the skin to protect a dog from flea and tick bites. These preventives are not affected by water.
- **Flea & Tick Collars:** The principle of the latest generation flea and tick collars is the same as spot-on treatments, but collars release small amounts of a preventive formula over time. A single collar may last for up to eight months. These collars may be water-resistant, but it is usually recommended to remove collars before swimming or bathing.

California-Davis, and Colorado State University.

“We anticipate this will yield more epidemiologic evidence that *Bartonella* can cause hemangiosarcoma,” says Dr. Breitschwerdt. “This could give us a powerful weapon against this devastating cancer.”

Efforts to protect dogs from ticks, fleas and other vectors that carry *Bartonella* remain important. “An important contribution we can

make to canine health is developing a vaccine to prevent infection with *Bartonella*,” Dr. Breitschwerdt says. “Dogs are our best sentinels to understand this insidious pathological bacterium.” ■

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