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## **Bartonella: New Science Revives a Neglected Infection**

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Bartonella species are very difficult human pathogens to study! This was the conclusion I presented in the final chapter of my doctoral dissertation, entitled “The epidemiology of bartonellosis and Lyme disease”, under the direction of Prof. Ed Breitschwerdt at North Carolina State University. In humans, Bartonella are very difficult to detect diagnostically; these bacteria don’t induce a predictable set of symptoms following infection; transmission by some insect vectors is hotly debated; and no standard treatment protocol has been established for bartonellosis.

After years of dedicating all of my brainpower to the genus Bartonella, I still can’t tell you what a negative diagnostic test result truly means, if a person will easily clear infection or start seizures in four months, or if that tick that bit you a couple weeks ago potentially gave you Bartonella. But, based on published literature and my own scientific bias, I can tell you what research has shown so far. So let’s first start with the basics: Bartonella species are rod-shaped, intracellular bacteria that are transmitted by blood sucking arthropods, including fleas, lice, sandflies, and reportedly ticks, as well as animal bites/scratches. The most well recognized manifestation of Bartonella is Cat Scratch Disease, which is an acute, self-limiting illness characterized by fever and lymph node swelling.

More recent reports, however, have suggested that some patients are unable to immunologically eliminate Bartonella infection from blood and/or tissues and may remain chronically infected for months to years with severe, debilitating symptoms. Those chronically infected with Bartonella have reported generalized fatigue, headaches, irritability, non-specific joint and muscle pain, and unexplained neurological issues, including hallucinations, visual deficits, and neuropathy. Many of these symptoms overlap with common signs and symptoms reported in Lyme disease. A recent published study showed that 41% of patients previously diagnosed with Lyme disease, chronic arthralgia, or myalgia had Bartonella DNA in their blood.

Some scientists suggest that Bartonella represent an important co-infection of Lyme disease and can be transmitted by ticks. Suspected co-infections with Bartonella and *Borrelia burgdorferi* following a tick bite have been reported, Bartonella has been detected in over a dozen species of ticks, and experimental transmission of Bartonella has been proven in one tick species. Other researchers argue that cases of bartonellosis may be potentially misdiagnosed as Lyme disease. What is certain is that rigorous scientific studies will clarify the significance of the Bartonella/*Borrelia* co-infection and the role of Bartonella infection in people with rheumatologic and neurologic symptoms.

The real question is: Why am I just hearing about Bartonella now? The existence of bartonellosis in humans and animals dates back hundreds of years; Bartonella quintana DNA has been identified in the dental pulp in the remains of soldiers in Napoleon’s Grand Army, and archeological evidence suggests the presence of Bartonella in human society over several millennia. Only recently have these

bacteria been acknowledged as emerging pathogens, due to advances in biotechnology that have allowed for the molecular detection of Bartonella in patient samples, and subsequently, newly discovered syndromes associated with infection.

New reports of Bartonella began to emerge in the 1990s, when infection was first documented as a cause of severe or fatal disease of the heart, central nervous system, lymph nodes, respiratory system, and GI tract in individuals with suppressed immune systems. Additional published cases have demonstrated severe liver disease due to infection following immunosuppression. Duke University Medical Center and the Mayo Clinic have described patients who were treated with immunosuppressive drugs and developed Bartonella-induced endocarditis, which is a severe condition characterized by inflammation of the heart's inner lining. These reports helped show that a weakened immune system, which also occurs in cancer patients, those on immunosuppressant drugs, young children, or aging adults, is a risk factor for severe clinical manifestations of Bartonella infection. However, within the past 10 years, research has suggested that even people with seemingly healthy immune systems can be chronically infected with Bartonella. So why can't a healthy immune system always eliminate Bartonella infection? Here's the theory:

When a person acquires Bartonella, the bacteria take up residence in the cells that line the blood vessels. Residence in these cells provides a great hiding spot for Bartonella to escape the host's immune system. From these cells, the bacteria can also cycle in and out of the blood stream. With access to the bloodstream, Bartonella can travel to and hide in various tissues throughout the entire body and produce a spectrum of disease in a variety of organ systems. Bartonella are considered 'stealth pathogens' because it is thought the bacteria can hide in different tissues and send signals to avoid the immune response for months to years.

The ability to reside anywhere in the body, in combination with an inadequate host immune response, is hypothesized to be the reason why we see such a broad range of symptoms associated with Bartonella infection. Within the scientific literature, the following symptoms and conditions have been reported in individuals infected with Bartonella:

- Non-specific: Fever of unknown origin, fatigue, weight loss, irritability, headaches, migraines, poor appetite
- Cardiovascular/hematologic: Endocarditis, myocarditis, pericarditis, hemolytic anemia, hypertension, pulmonary thromboembolism, vasculitis, cardiac arrhythmias
- Neurological: Hallucinations, visual deficits, peripheral neuropathy, polyneuropathy, neuroretinitis, multiple sclerosis-like symptoms, transverse myelitis, panic disorder, agitation, anxiety, treatment resistant depression, encephalopathy, areflexia
- Rheumatologic: Rheumatoid arthritis, chronic fatigue, myositis, myalgia, systemic vasculitis, Henoch- Schonlein purpura, systemic lupus erythematosus, osteomyelitis, uveitis

As noted earlier, a recent study showed that 41% of individuals with rheumatologic and autoimmune-like symptoms had Bartonella DNA in their blood. Unfortunately, therapy for autoimmune and

rheumatologic disorders relies on immunosuppression, which we already know can result in severe clinical manifestations in Bartonella infected individuals. It is, therefore, critical to rule out Bartonella infection prior to immunosuppressive therapy to properly treat rheumatologic and autoimmune disorders and avoid major, preventable complications.

### **Diagnostics:**

Detection of Bartonella infection in humans has always been challenging due to low sensitivity of the available diagnostic laboratory tests. Historically, Bartonella infection was diagnosed using IFA serology. This test specifically detects antibodies that may be produced following infection with Bartonella. However, because Bartonella have many properties that allow it to successfully evade the immune system, not all infected individuals produce antibodies against Bartonella, and studies have shown that up to 85% of chronically infected individuals may test negative for antibodies through IFA serology.

A more sensitive diagnostic approach uses PCR to detect Bartonella DNA in tissues or blood. However, Bartonella often infect people at very low levels that cannot be detected using standard PCR. As scientists at NCSU have shown, an enrichment blood culture is needed to grow Bartonella to detectable levels for PCR to overcome the risk of a false negative result. Bartonella-alpha-Proteobacteria-growth-medium (BAPGMTM) is a medium that is able to culture all pathogenic species of Bartonella. Bartonella ePCRTM using the BAPGM medium is available exclusively through Galaxy Diagnostics, Inc.

Because studies suggest that Bartonella prefer to reside in the tissues that line the blood vessels and only periodically enter into the blood, testing for Bartonella at a single point in time can result in false negatives, simply because the bacterium is residing in the tissues and not the blood at the time of the draw. Research have shown that serial testing by obtaining and testing three sequential blood specimens during a 7-8 day period (e.g. M-W-F) is important to enhance detection of Bartonella infection.

Because infection is unpredictable and complex, accurate and highly sensitive diagnostic tests are the resource both researchers and clinicians need to clarify the clinical course and epidemiologic features of Bartonella infection. Innovative, highly sensitive tests are the key to reduce misdiagnosed conditions and chronic suffering. And with over 20+ years of research experience, 100+ publications on Bartonella, including dozens of publications on human bartonellosis, Galaxy Diagnostics, Inc. has the technology and access to the expertise to solve these key issues using Bartonella ePCR testing. We invite patients and physicians to utilize our knowledge and diagnostic capabilities for addressing the role that Bartonella is playing in at-risk patients with unexplained disease.

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