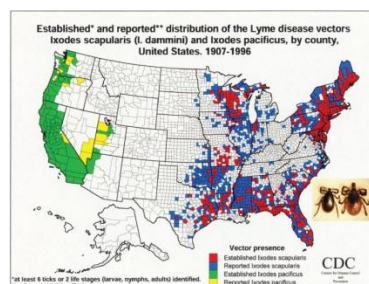


Lyme and Lyme-like disease – the new epidemic

By: Tracie Leonhardt, DO

Lyme is caused by *Borrelia Burgdorferi* spirochete. Its life cycle begins with larval ticks transmitted by the bite of an infected *Ixodes* tick. These ticks feed upon small mammals such as the white footed filed mice, catbirds, squirrels, opossum, and other small animals, and then mature into nymphs. In addition to transmitting Bb into various animal hosts, the black legged tick can also transmit strains of other infections such as; *Anaplasma*, *Bartonella*, *Ehrlichia*, or *Babesia*. Lyme borreliosis has a worldwide distribution and is the most common vector-borne disease in the United States according to the CDC. There are approximate 30,000 cases recorded per year and an estimated 300,000 cases documented. The CDC has now upgraded Lyme disease to official epidemic status in the United States. In January 2016, it was reported by Harvard University that Lyme disease carrying ticks are now in half of all US counties.¹ There are greater than 20 species worldwide of *Borrelia* species, with 7 identified species described in the U.S. The species so far identified in the US are *B. Burgdorferi*, *Americana*, *andersonii*, *bissettii*, *californiensis*, *kurtenbachii* and most recently *B. Mayonii* in the Midwest.² Of these at least 5 *Borrelia* species have been associated with Lyme disease in the US: *Bb sensu stricto*, *Americana*, *andersonii*, *bissettii*, and *myaonii*. The additional frustration of proper diagnosis and co-infections arise, as very few ticks are carrying only one infectious vector. For example, the well-known blacklegged tick (*Ixodes scapularis*) not only can carry the Lyme spirochete, but may also be carrying anaplasmosis, babesiosis and Powassan disease.³ This makes diagnosis and identification much more difficult. Dr. Richard Horowitz stopped calling this Lyme disease and named this phenomenon Multiple Systemic Infectious Disease Syndrome or MSIDS.⁴ According to the US Department of Health and Human Services there is the black legged tick, lone star tick, brown dog tick, ground hog tick, gulf coast tick, rocky mountain wood tick, soft tick, western black legged tick and the American dog tick that can carry tick borne infections. This seems to fit the diagnosis much better as very few chronic lyme patients only have Lyme disease. These infections attack the immune system, stimulate an inflammatory cascade and can attack multiple systems in the body, including the skin, brain, nervous tissue, and heart.





Erythema Migrans

Lyme the infection

In 1988, Asbrink and Hovmark conceived of untreated Lyme Disease as having three phases. Phase 1 represented early, localized infection, the hallmark of which was erythema migrans (EM) and its variations. Phase 1 included fever, muscle aches, headache, nausea and fatigue. Phase 2 witnessed early dissemination of the infection with worsening of malaise and fatigue, as well as the appearance of new cardiac and arthritic signs and symptoms including AV heart block, myocarditis, migratory joint pains and synovitis. Phase 3 saw late dissemination with the appearance of polyneuropathy, neurocognitive and neuropsychiatric abnormalities and meningitis, as well as chronic arthritis and debilitating fatigue.⁵

Lyme and the Inflammatory Pathways

Inflammation is the body's attempt at self-protection, its aim being to remove harmful stimuli, including damaged cells, irritants, or pathogens so the body can begin the healing process. In Lyme and its co-infections incite a hyper-response of cytokine formation. Cytokines are produced when the immune cells are stimulated by infection, oxidizing agents, cytokines, toxins, and other agents. Once the immune cells are stimulated, NF-KB causes genetic programming for the production of cytokines and the activation of the leukocytes. Cytokines are proteins made of various types of white blood cells with their function being to make antibodies work more effectively, increase WBC activity, recruit other WBC to the site of infection and to decrease viral and bacterial replication. With Lyme and other related infections – there is an overproduction of cytokines inducing an excessive inflammatory response leading to chronic inflammation. This may manifest itself as a suppressed immune system, pain, reduced hormonal production from the thyroid and adrenal glands, sleep disturbances, cognitive decline, fatigue, myalgia's, and depression.⁶

The dysregulation of cytokines and chemokines is a central feature in the development of neuroinflammation, neurodegeneration, and demyelination both in the central and peripheral nervous systems. This process can lead to activation of the microglia, which may mediate neuronal and glial cell injury and death thru the production of the proinflammatory factors such as cytokines.

About 15 % of the patients with Lyme disease develop peripheral and central nervous system symptoms and involvement. Research indicates that the activation of the inflammatory pathways play a causal role in the often debilitating and painful symptoms.⁷ Lyme or lyme like diseases can cause arthritis, carditis,

and neurologic deficits. When the nervous system is involved it is called Lyme neuroborreliosis (LNB).⁸ Microglia and astrocytes are key players in the immune responses within the CNS. Studies have shown that microglia and astrocytes express Toll-like receptors that play a major role in innate immune responses against microbial pathogens.⁹ Peripheral Nervous System involvement can include facial nerve palsy (bell's palsy), neurogenic pain radiating along the back into the legs and feet, limb pain, sensory loss, or muscle weakness. Central nervous system involvement may manifest as headache, fatigue, memory loss, learning disability, depression, meningitis, and encephalopathy. Significantly elevated levels of the inflammatory mediators interleukin-6 (IL-6), IL-8, CCL2, and CXCL13 were found as well and increased cell counts of white blood cells in the cerebral spinal fluid.¹⁰ Chemokines such as IL-8 and CCL2 are known to mediate the influx of immune cells in the CNS in the presence of bacterial meningitis. CXCL12 is known to be the major determinant of B cell recruitment into CSF during neuroinflammation.¹¹ In animal models, upon examination of the dorsal root ganglia, it showed inflammation with neurodegeneration, along with apoptosis of neuronal and satellite glial cells. Lyme, as a pathogen, also turns on the coagulation system by directly turning on the clotting cascade to increase the formation of fibrin leading to hypoxia. This is why the fibrinogen levels may increase in Lyme patients. This process of the activated coagulation pathway is stimulated by the inflammatory cytokines. Some of the pathogens that will activate the inflammatory and coagulation pathway are HHV6, EBV, CMV, mycoplasma, HS1 and HS2, chlamydia, brucellosis, Babesia, Ehrlichia, Bartonella and Borrelia; many of which are co-infections of Lyme disease. This becomes important when talking about the difficulty in treatment these infections and their resistance against treatment. Many bacteria and viruses use fibrin to form protective barriers around themselves referred to as biofilms or cyst formation. The layer of fibrin covering the microbe makes it almost undetectable by the immune system.¹²

Biofilms and the difficulty in treatment

A biofilm is an accumulation of microbial cells that is irreversibly associated with a surface and enclosed in a matrix of primarily polysaccharide material.¹³ I usually describe this to my patients as the goo that is left over after pulling up duct tape. Biofilms are the predominant phenotypes in natural and pathogenic ecosystems. As a pathogenic mechanism they serve as a population-level virulence factor to provide the infectious organism with virulence traits that a single organism cannot possess. These traits are protective to the invading organism and allow them to persist in the host despite the innate and adaptive immune systems. Biofilms usually are associated with chronicity or persistence – as opposed to acute virulence traits such as toxin production. Most chronic infectious disease processes are associated with biofilm production. The biofilm allows for the infection to attach to the host. The biofilm protects the organism from the host's adaptive immune response, along with being attacked by phagocytes. Biofilms also provide an ideal setting for elevated levels of gene transfer for the invading organism. The gene transfers occur since nearly all of the chronic pathogens that form biofilms contain inducible-energy that require horizontal gene transfer mechanisms that serve a nonnutritive role as opposed to using the DNA only as a food source. Horizontal gene transfer (HGT) is defined as the movement of genes between two unrelated cells usually in a unidirectional manner.¹⁴ This allows

bacteria to transmit genes vertically to daughter cells, or by HGT. Three forms of HGT have been classified: transformation, conjugation, and transduction.

Diagnosis of Lyme Disease

There is a lot of controversy on how to diagnose Lyme. The testing methods available are less than ideal with low sensitivity levels. The standard of care has a two tier serological testing. First tier screening is performed by an ELISA which should be performed in all suspected patients that believe they have an exposure 3-4 weeks after initial exposure. This is when Lyme –specific IGM serology is also detectable followed by months later by a Lyme-specific IGG response. The ELISA test has a low sensitivity and therefore, many physicians will check Western Blot. A study published in The British Medical Journal found that the overall sensitivity of the combined ELISA-western blot was only 56 percent.¹⁵ The issues with Western Blot do occur with the strain that the lab uses as there are multiple strains of *Borrelia* present in the United States, and there are over three hundred strains worldwide. *Borrelia*-specific bands reflect outer surface proteins on the surface of the organism that are seen more often in Lyme disease than in other infections. These bands include 23kDa (Outer surface protein C – OspC), 31kDa (OspA), 34kDa (OspB), 39kDa, and 83-93kDa. It is thought that if any of these bands are present on Western Blot, that there is a high likelihood that the patient may have been exposed to Lyme. Most commonly strain used for testing is the B31 strain; however, some think that the 297 strain is more reliable. There is also PCR testing (Polymerase chain reaction), a DNA test with the limitation that it may require multiple samples over time.^{16 17} Most believe that Lyme is a clinical diagnosis, and that lab results serve to support the clinical diagnosis. There are the supporting tests such as complement 3A and 4A levels and CD 57 counts. Complement split products are reportedly elevated in patients with acute Lyme disease. A Study by Ray Stricker showed that patients with predominantly musculoskeletal symptoms of Lyme disease had significantly increased levels of C4a compared to controls. The study also showed that response to treatment with antibiotics was associated with a significant reduction in C4a levels.¹⁸ Another study showed that patients with chronic Lyme disease had decreased levels of CD 57 lymphocytes over 10 years. This study concluded that Chronic Lyme disease is associated with a persistent immunologic defect that prevents the infection from being cleared by the immune system.¹⁹ CD 57 is a marker of nature killer cell differentiation, and has been most widely explored as a marker of replicative senescence on T cells.²⁰ CD 57 is still not fully known and is not recommended to use by the CDC; however, many physicians that treat Lyme everyday use the CD 57 count to monitor treatment. On the horizon in phase II trials is nanotrap technology. This will have a high sensitivity of over 90% and specificity. This test employs nanotrap particles to concentrate urinary OspA and use a high specific anti-OspA monoclonal antibody as a detector of the C-terminus peptides.²¹

Treatment Options for Lyme

There is a lot of theories of how to treat Lyme disease. Everyone agrees that for the acute case to treat with antibiotics for 2-4 weeks. But, for chronic Lyme there is a lot of disagreement. Accepted therapy is long term antibiotics, but do you use one or three to four? Do you use an intracellular antibiotic, a cyst buster or an outer membrane antibiotic. The International Lyme and Associated Diseases Society

(ILADS) recommend antibiotic therapy – although some are advocating higher doses and combination therapies. It is recommended to start prophylaxis treatment for a black legged tick bite. Treatment options for a EM rash is 20 days of azithromycin, cefuroxime, doxycycline or amoxicillin. Long term treatment is sometimes required for patients with chronic Lyme. It is thought that Lyme spirochete can penetrate into the bone marrow and this is one of the methods that make it difficult to kill.²² According to a study done by Dr. Christa Muller-Sieberg found that stem cell lived as little as 5 months and others lived to over 3 years. If this is true and Lyme can penetrate stem cells, this may account for some of the relapses with shorter treatment.

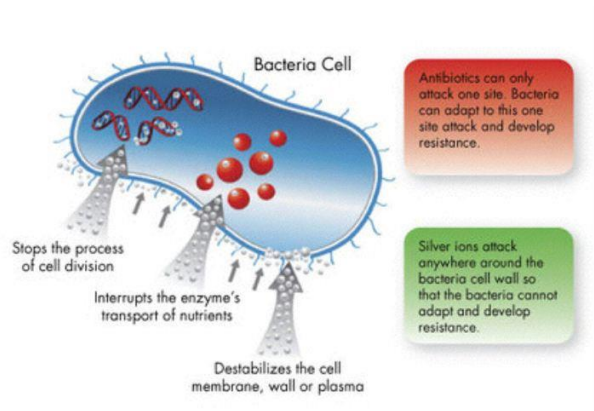
Below is a table of antibiotic treatment options

Cell Wall Form	Cystic Forms	Intracellular Location
Penicillins <ul style="list-style-type: none"> • Amoxicillin • Augmentin • Bicillin (IM) 	Plaquenil	Macrolides <ul style="list-style-type: none"> • Zithromax • Biaxin
Cephalosporins <ul style="list-style-type: none"> • Ceftin • Omnicef • Cedax • Suprax 	GSE	Quinolones <ul style="list-style-type: none"> • Cipro • Levaquin • Avelox • Factive
IV Cephalosporins <ul style="list-style-type: none"> • IV Rocephin • IV claforan 	Flagyl Tindamax	Rifampin Tetracyclines <ul style="list-style-type: none"> • Doxycycline • Minocycline • Tetracycline HCL
Other IV Medication <ul style="list-style-type: none"> • IV Vancomycin • IV Primaxin 		Other IV medication <ul style="list-style-type: none"> • IV doxycycline • IV Zithromax • IV Levaquin/Avelox • IV Rifampin

Alternative therapies for Lyme

Many patients are against prolonged antibiotic usage – so what are their alternatives. There are several immune supportive herbal medication such as cordyceps and reishi– while not curative. Byron White has several preparations for Lyme and the co-infections. These are herbal tinctures that are very potent and need to be used with a trained practitioner and in small doses. Ozone therapy has been shown to be beneficial as it increases the immune response. Ozone has been shown to kill bacteria and virus on contact and prevents viruses from adhering to the cell wall. The most effective alternative treatment we have found is IV silver hydrosol with Argentyn 23. Silver is well known to be a broad spectrum antimicrobial agent, but has also been reported that it has anti-viral, anti-inflammation, anti-biofilm activities and enhanced wound healing.²³ Some studies suggest that the particle size, shape, surface charge, surface coating, solution chemistry, and solubility affect silver's toxicity.²⁴ Silver is considered virostatic – stopping the replication of the virus on contact.²⁵ Silver is processed by the liver in which

the co-factor in the liver for silver elimination is selenium dependent. Therefore, it is suggested to make sure the patient is taking selenium while taking silver.²⁶ With silver we usually start with oral doses to clear the spirochete and the stealth form (L-form). We use only 23 ppm silver hydrosol as an IV drip at a slow rate. In our practice, using silver in high doses has been very effective in not only having our patient's symptom free, but also their labs indicating that they are infection free. Our longest patient so far has been symptom free for 4 years.



Silver Hydrosol Mechanism of Action

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