Diagnosis and Therapy of Chronic Systemic Co-infections in Lyme Disease and Other Tick-Borne Infectious Diseases

by Prof. Garth L. Nicolson*

Abstract

Often Lyme disease (LD) patients are initially diagnosed with other illnesses, such as Chronic Fatigue Syndrome. The diagnosis of LD should be based on clinical and laboratory data as well as the likelihood of exposure to the LD spirochete. Virtually all LD patients have multiple co-infections. In addition to the *Borrelia burgdorferi*, the majority of LD patients are also infected with tick-borne mycoplasma, rickettsia, and/or protozoa. There are a number of considerations when undergoing therapy for the multiple infections found in chronic LD, including whether to use traditional antimicrobial as well as integrative nutraceutical approaches. Chronic LD requires long-term therapy, including antibiotic/antiprotozoan therapies and dietary supplements to restore immune and gastrointestinal systems as well as mitochondrial function.

Lyme disease is the most common tick-borne disease in North America and has been reported in 48 US states and in Eastern Canada. First described in Old Lyme, Connecticut in 1975, the infection is caused by a tick bite and the entry of the spiral-shaped spriochete *Borrelia burgdorferi* (Bb) and other co-infections.[1] Bb and its co-infections have been carried into new habitats by a variety of ticks, such as the deer, black-legged, lone-star, and bear ticks, and their vectors, such as birds, deer, rodents, and other mammals. After incubation for a few days to a month, the LD spriochete and co-infections migrate through the subcutaneous tissues into the lymph and blood where they can travel to near and distant host sites.[2] Transplacental transmission of Bb and co-infections can occur in pregnant animals, including humans, and blood-borne transmission in humans by blood transfusion is likely but unproven. The tick-borne LD co-infections can and usually do appear clinically at the same time.

Often LD patients are diagnosed with other illnesses, such as chronic fatigue syndrome (CFS) or rheumatoid arthritis (RA). Since the signs and symptoms of LD overlap with other chronic conditions, this is not unusual. However, many patients with LD have not received an adequate diagnosis for years, and during this period, ineffective treatments may have contributed to the refractory nature of the disease.

Clinical and Laboratory Diagnosis of Tick-Borne *Borrelia burgdorferi* Infections

About one-third of LD cases start with the appearance of a round, red, bulls-eye skin rash *(erythema migrans)* at the site of the tick bite, usually within three to 30 days.[2] Within days to weeks, mild flu-like symptoms can occur that include shaking chills, intermittent fevers, and local lymph node swelling. After this localized phase, which can last weeks to months, the infection(s) can spread to other sites (disseminated disease), and patients then show malaise, fatigue, fever and chills, headaches, stiff neck, facial nerve palsies (Bell's palsy), muscle and joint pain, and other signs/symptoms.

LD can eventually become persistent or chronic and involve the central and peripheral nervous systems as well as ophthalmic, cardiac, musculoskeletal, and internal organ invasion. At this late chronic stage, rheumatoid arthritis, neurological impairment with memory and cognitive loss, cardiac problems (mycocarditis, endocarditis causing palpitations, pain, bradycardia, etc.), and severe chronic fatigue are often apparent.[2-4] As mentioned

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above, the signs/symptoms in the late chronic phase of the disease usually overlap with other chronic conditions, such as CFS, fibromyalgia syndrome, rheumatoid arthritis, among others,[5] causing confusion in the diagnosis and treatment of the chronic phase in LD patients. Some contend that this late phase is not even related to LD, resulting in failure to successfully identify and treat the chronic condition. The involvement of co-infections, such as Mycoplasma species and other co-infections, in causing chronic signs/symptoms in patients has not been carefully investigated; however, such infections on their own have been shown to produce comparable signs/symptoms.[6]

As with many chronic illnesses, diagnostic laboratory testing for LD at various clinical stages is, unfortunately, not full-proof, and experts often stress the need to diagnose LD with a checklist of signs and symptoms and potential exposures, along with multiple laboratory tests.[2,7] The laboratory tests used for LD diagnosis include detection of Bb surface antigens by enzyme-linked immunoassay (EIA), immunofluorescent assay (IFA), and Western immunoblot of Borrelia proteins. Alternatively, polymerase chain reaction (PCR) for Borrelia DNA has been used to detect the DNA of the intact organism in blood.

A true-positive test result usually consists of more than one positive test from the above list, usually EIA followed by Western immunoblot. The problem with these tests is that they are blood tests requiring the presence of antibodies or Borrelia proteins in the blood, or they are dependent on the spirochete and thus its DNA being present in the blood (PCR). Some of the tests, such as serology testing for antibodies against Bb antigens, show cross-reactivity with other microorganisms and, in some cases, are only useful four to six weeks after onset of signs/symptoms; thus, the quality of the tests can vary. The most sensitive type of test (PCR) requires that the spirochete be released into the blood where its DNA can be detected, and this only occurs occasionally, such as within the first week of antibiotic administration.

Other tests that are offered for LD have been criticized. For example, diagnosis of LD based on culture of *B. burgdorferi* is completely unreliable.[7] One laboratory offers a one-step Lyme antigen urine test (LUAT), but some researchers have criticized this test for its high rate of false-positive tests.[8] Similarly, some IFA tests are suspect because they are almost universally positive. Most consider a patient positive if Bb antigens (EIA plus Western Blot analysis) are present in blood serum in more than one test, or the patient is PCR-positive for Bb.

Table 1. Treatment of Lyme Disease During the Different Stages of the Disease[12,13]

Clinical Stage	Time	Primary Treatment	Alternative Treatment
Early localized	3-30 days	doxycycline	erythromycin
		amoxcillin	clarithromycin
		cefuroxime axetil	azithromycin
Early disseminated	1-12 wks	doxycycline	erythromycin
		amoxcillin	clarithromycin
		cefuroxime axetil	azithromycin
with CNS involvement		ceftriaxone (iv)	penicillin G (iv)
			doxycycline (iv or po)
Late disseminated	>2 months		
with arthritis		amoxcillin	penicillin G (iv)
		doxycycline	doxycycline (iv or po)
with CNS involvement		ceftriaxone (iv)	penicillin G (iv)
			doxycycline (iv or po)
with cardiac involvement		ceftriaxone (iv)	
		amoxcillin	

Diagnosis of Tick-Borne Co-Infections: Mycoplasma, Babesia, Ehrlichia, and Others

Co-infections complicate the diagnosis and signs/symptoms of LD. These infections can also occur in various combinations. For example, another tick-borne infection is caused by the intracellular protozoan *Babesia* spp., first described in domestic animals in Romania.[9] There are over 100 species of the genus Babesia, but most infections in humans in North America are caused by *Babesia microti* and in Europe by *Babesia divergens* and *Babesia bovis*. About 20-40% of cases of LD show Babesia co-infections. When both infections are present, the number of signs/symptoms, their severity, and the duration of illness can be greater in the early stages of disease,[9] including high fever, chills, generalized weakness, gastrointestinal symptoms (anorexia, nausea, abdominal pain, vomiting, diarrhea, among others), anemia, muscle and joint pain, respiratory problems, and dark urine. This combination of infections can be lethal in some patients (about seven percent of patients can have disseminated intravascular coagulation, acute respiratory distress syndrome, and heart failure), but the majority of patients with *Babesia* spp. have the chronic form of the infection. In Babesia infections, patients can show mild-to-severe hemolytic anemia (probably correlating with the protozoan colonization of erythrocytes, which can be seen by experienced individuals in blood smears) and a normal to slightly depressed leukocyte count.[9] However, this is usually not seen in patients who have progressed to the chronic phase of the disease.

We and others[10] have found that the most common co-infection with Bb are various species of Mycoplasma. Approximately 60-75% of LD patients also have mycoplasmal co-infections (*Mycoplasma fermentans* > *Mycoplasma hominis* > *Mycoplasma pneumoniae, M. genitalium, M. penetrans,* other species). In some cases, multiple

mycoplasmal infections are present in LD patients. The presence of mycoplasmal infections complicates the diagnosis and treatment of LD, and some of the generalized signs/symptoms found in Borrelia-positive patients are also found in Mycoplasma-positive patients.[5,6]

Like the *Bb* spirochete, mycoplasmas are found at intracellular locations in various tissues and are only rarely found free in the blood. This can make detection difficult, and, in some patients, the appearance of Bb and various mycoplasmas in their white blood cells can be cyclic. We recommend testing for mycoplasmal infections in LD, using the most sensitive PCR procedures to detect DNA in white blood cells.[5,6,11] In addition to LD, mycoplasmal infections have been found at high incidence (40-60%) in CFS, Fibromyalgia syndrome, rheumatoid arthritis, Gulf War Illness, and neurodegenerative diseases.[5,6,11,12] These are emerging infections, and the medical community is just beginning to respect the involvement of this type of co-infection in many clinical conditions.

Another co-infection found in some LD patients is a rickettsial infection caused by Ehrlichia species.[2,3] These small, gram-negative, pleomorphic, obligate, intracellular infections are similar to mycoplasmas in their structures, intracellular locations, and resulting signs/symptoms. Commonly found species are *E. chaffeensis* and *E. phagocytophila,* and these microorganisms can cause signs/symptoms within one to three weeks of exposure, such as fever, shaking chills, headache, muscle pain, and tenderness, and, less commonly, nausea, vomiting, abdominal pain, diarrhea, cough, and confusion.[3] Laboratory features include mild to moderate transient hemolytic anemia, decreases in white blood cell count (leucopenia, thrombocytopenia), elevated erythrocyte sedimentation rate and, sometimes, increases in liver enzymes and, less often, increases in blood urea nitrogen and creatinine. Serology is usually only positive after one to two weeks with the limitations discussed above. Since culturing the microorganism is not practical, antibody and PCR testing have been used for confirmation of the infection.[3]

Chronic Systemic Co-infections

LD patients are at risk for a variety of other opportunistic infections, including other bacterial infections as well as viral and fungal infections. These can complicate diagnosis and treatment, but they may be a problem principally in the late, chronic phase of the disease. Late-stage patients with neurological manifestations, meningitis, encephalitis, peripheral neuropathy, and other signs/symptoms may have complicated co-infections that are not recognized or treated by their physicians.

Treatment of LD Borrelia and Co-Infections

Most LD patients do well on combinations of antibiotics plus nutritional and nutraceutical support. Experts agree that LD is much easier to treat in the earlier phases, but some of the co-infections can be difficult to treat, especially if the disease is in the late chronic stage. The most common recommendations for the treatment of LD Borrelia and co-infections involve antibiotics that can effectively suppress early localized or early disseminated LD Borrelia.[2-4] A variety of antibiotics in two-week regimens show good activity against early-stage Borrelia infections, such as combinations of doxycycline plus amoxicillin, doxycycline plus penicillin V and amoxicillin or penicillin V plus cefuroxime axetil, in that order, in terms of effectiveness and expense,[2,13] although some reports indicate that the latter antibiotics are just as effective as the doxycycline combinations.[14,15] Also, doxycycline also shows good activity against most species of Mycoplasma and Ehrlichia, and it also shows good penetration into the central nervous system (CNS). Doxycycline should not be used in children under the age of eight years, but some have suggested that short-duration treatments (two weeks) at pediatric doses are very useful.[13] Alternatives include the use of erythromycin, but most experts do not consider this a first-line treatment for LD Borrelia.[2,13]

A major problem in the treatment of LD is finding effective treatments of the late chronic stage, especially when they involve the CNS. Table 1 shows the antibiotics useful for treating LD based on the clinical situation.[13-15] Since with time (late stage), Bb infections occur intracellularly as cystic or persistent forms, Plaquenil, Falgyl, or Tinidazole should be added along with a macrolide (azithromycin, Biaxin, or Dynabac) and/or fluoroquinolones (ciprofloxacin, gatifloxacin, levofloxacin, ofloxacin).[13-17] ➤

Table 2. Combination Treatments for Lyme Borrelia Plus Co-Infections[17]

Lyme Borrelia	*Mycoplasma/Ehrlichia*	*Bartonella*	*Babesia*
Amox+Probenecid+ Macrolide+Plaquenil ±Flagyl/Tinidazole	+Doxycycline	+Septra	+Mepron +Malarone +Lariam
Bicillin+Macrolide+ Plaquenil ±Flagyl/Tinidazole	+Doxycycline	+Septra	+Mepron +Malarone +Artemesia +Lariam
Cephalosporin (po/iv)+ Macrolide+Plaquenil ±Flagyl/Tinidazole	+Doxycycline	+Septra	+Mepron +Malarone +Artemesia +Lariam
Doxycycline+ Plaquenil ±Flagyl/Tinidazole	+Ciprofloxacin	+Septra +Rifampin	+Lariam +Malarone +Artemesia
Macrolide+Plaquenil ±Flagyl/Tinidazole	+Doxycycline	+Septra +Quinolone	+Mepron +Malarone +Artemesia +Lariam

With antibiotic treatment, Herxheimer reactions (or "die-off" reactions involving chills, fever, night sweats, muscle aches, joint pain, short-term memory loss, and fatigue or a general worsening of symptoms) usually occur for days to weeks due to release of bacterial cell wall degradation products and stimulation of interleukins or chemical messengers that cause worsening of some signs/symptoms.[16,17]

To overcome Herxheimer reactions or other adverse responses, IV antibiotics have been used for a few weeks – followed by oral antibiotics. Oral Benadryl (diphenhydramine, 50 mg) taken at least 30 minutes before antibiotics, and lemon/olive drink (one blended whole lemon, one cup fruit juice, one tablespoon olive oil – strain and drink liquid) have proved useful.[16] This period usually passes within a few weeks and differs from allergic reactions that can cause immediate rashes, itching, swelling, dizziness, breathing trouble, and other problems. For LD, the dosing for pediatric use has been worked out.[2]

Antibiotic Therapy for Co-Infections of Borrelia, Mycoplasma, Babesia, and Others

For patients with co-infections of Borrelia plus Mycoplasma species, the therapy should be the same as in Table 1 (with doxycycline), but the duration of therapy must be increased. The reason for this is that slow-growing mycoplasmal infections are not readily susceptible to antibiotics, and thus the therapy must be more gradual.[6,16,17] Some patients with Mycoplasma co-infections may benefit from combinations of antibiotics other than those listed in the table, such as adding additionally azithromycin or a floxacin, especially if there are limited responses.[16] These can be worked into the regimen slowly over weeks, if necessary. The protocol for infections involving Borrelia plus Mycoplasma species should be continued for at least six months.[17]

When Babesia infections are present as co-infections with Borrelia, patients can be treated with quinine (Quinamm) and clindamycin (cleocin).[9] For co-infections with Mycoplasma or Ehrlichia species, doxycycline should be added to the antibiotic regimen.[3] Dr. Richard Horowitz has presented a scheme for treating co-infections in LD,[19] and I have added advice on Mycoplasma/Ehrlichia co-infections (Table 2). If *Chlamydia pneumoniae* is also present, then two penetrating antibiotics active against these microorganisms should be considered, such as doxycycline plus a fluoroquinolone (levofloxacin, ofloxacin, or gatifloxacin).

General Nutritional Considerations When Undergoing Therapy

LD patients are often immunosuppressed and susceptible to opportunistic infections, so proper nutrition is imperative.[17] Patients should not smoke or drink alcohol or caffeinated products. Fresh fluids, lots of juices (such as Juice Plus), or pure water are best. It is important that patients avoid high sugar and fat foods, such as military (MRE) or other fast foods and acid-forming, allergen-prone, and system-stressing foods, or high sugar/fat junk foods. Increase intake of fresh vegetables, fruits and grains, and decrease intake of fats and simple or refined sugars that can be immunosuppressive. Cruciferous vegetables, soluble fiber foods, fish, and whole grains are useful. In some patients, exclusive use of "organic" foods has been beneficial. For heavy metal removal, Garlic Plus (Longevity) has been proposed, and we find the use of Detoxamin suppositories useful. For help with bowel bacteria and bladder infections, many recommend D-mannose (Biotech). This natural sugar inhibits binding of bacteria to biological membranes.

Chronic illness patients are often depleted in vitamins (especially B complex, C, E, CoQ-10) and certain minerals.[16] These illnesses often result in poor absorption. Therefore, high doses of some vitamins are useful; others, such as vitamin B complex, cannot be easily absorbed, so sublingual natural B-complex vitamins should be substituted. General vitamins plus extra C, E, CoQ-10, beta-carotene, folic acid, bioflavoids, and biotin appear to be best, and L-cysteine, L-tyrosine, L-glutamine, L-carnitine, malic acid, and flaxseed or fish oils have been used as supplements. Certain minerals are depleted in chronic illness patients, such as zinc, magnesium, chromium, and selenium. Thus, extra vitamins and minerals have been used, especially if patients are removing heavy metals with chelating agents. Vitamins and minerals must not be taken at the same time of day as antibiotics (or oxygen therapy), because they can affect absorption.

Yeast/Fungal Overgrowth While on Antibiotics

Yeast overgrowth can occur, especially in females (especially vaginal infections) during antibiotic therapy. Gynecologists recommend Nizoral, Diflucan, Mycelex, or anti-yeast creams. Metronidazole (Flagyl, Prostat) has been used to prevent fungal or parasite overgrowth, or other antifungals (Nystatin, Amphotericin B, Fluconazole, Diflucan, or Pau d' arco, seven capsules/twice a day) have been administered for fungal infections that can occur while on antibiotics. Some patients have as their principal problem systemic fungal infections that can be seen using dark field microscopy of blood smears. For superficial fungal infections, such as fungal nail, a topical mixture of Laminsil in 17% DMSO twice a day is effective. As mentioned above, *L. acidophilus* mixtures are used to restore gut flora. Bacterial overgrowth can also occur, for example, between cycles of antibiotics or after antibiotics have been stopped.[16]

Nutraceutical approaches to controlling yeast infections include Pau d'arco, grapefruit extract, olive leaf, caprylic acid, garlic extract, and oregano oil. Diet is especially important in controlling yeast overgrowth, and the dietary instructions above should be followed, such as the elimination of most simple sugars from the diet.[16-18]

Oxidative Therapy for Chronic Lyme Disease Co-Infections

Borrelia, Mycoplasma, Ehrlichia, and other infections are mostly intracellular and should be considered borderline anaerobic infections

that grow and survive better in low oxygen environments. Oxidative therapy can be useful in suppressing a variety of anaerobic infections, but this approach should be considered experimental and only palliative. We recommend several weeks to months of Hyperbaric Oxygen (1.5-2.0 ATM, 60 minutes) treatments, because these are well-tolerated by most patients with chronic infections.[16] Alternatively, American Biologics Dioxychlor, IV ozone, or hydrogen peroxide might be useful but should only be undertaken with experienced physicians. Some patients have used peroxide baths with two cups of Epsom salt in a hot bath or Jacuzzi. After five minutes, two to four 16 oz. bottles of three-percent hydrogen peroxide are added. This is repeated two to three times per week; but no vitamins may be taken four hours before the bath. The hydrogen peroxide is added after skin pores open. This appears to have some benefit to patients, especially those with skin/muscle problems.

Hydrogen peroxide can also be directly applied to skin after a work-out or hot shower/tub. In this case, the hydrogen peroxide is left on for five minutes and then washed off. For oral irrigation, one part three-percent hydrogen peroxide with two parts water can be used like a mouth wash three times per day.[16] Most chronic illness patients have periodontal problems, and oral infections and bone cavitation infections are common.

Replacement of Gut Flora; Immune Modulators; and Natural Remedies

Patients undergoing treatment with antibiotics and other substances risk destruction of normal gut flora, and this can result in overgrowth of less desirable bacteria. To supplement bacteria in the gastrointestinal system, live *Lactobacillus acidophilus* in capsules or powder have been strongly recommended. Mixtures of *Lactobacillus acidophillus, L. bifidus, B. bifidum, L. bulgaricus,* and fructoologosaccharides to promote growth of these probiotics in the gut have also been used. *L. acidophillus* mixtures (above 2.5-3 billion live organisms) should be taken three times per day. For irritable bowel, the nutraceutical Calm Colon (Samra) has proven to be very effective in clinical trials. A very good probiotic mixture is Theralac (www.theralac.com). In addition, to improve digestion and especially absorption, enzyme mixtures have proved useful. The best known of these is Wobenzym.

A number of natural remedies, such as ginseng root, herbal teas, lemon/olive drink, and olive leaf extract with antioxidants are sometimes useful, especially during or after antibiotic therapy. More important examples are immune modulators, such as bioactive whey protein (ImuPlus, www.imuplus.com; Immunocal, ImmunoPro), transfer factor (4-Life Transfer Factor, Immuni-T), or MGN3. Some additional remedies are: olive

leaf extract (many sources), NSC-100, and Laktoferrin. These products have been used to boost immune systems. Although they appear to help many patients, their clinical effectiveness in chronic-illness patients has not been carefully evaluated. They appear to be useful during therapy to boost the immune system or after antibiotic therapy in a maintenance program to prevent relapse and opportunistic secondary infections.

Lipid Replacement Therapy for Chronic Infections and Restoring Mitochondrial Function

Lipid Replacement Therapy is useful in providing membrane lipids in unoxidized forms to repair nerve and mitochondrial membranes that are damaged by heavy metals, chemicals, and infections.[20] For LD patients, we recommend the oral supplement Healthy Aging containing NTFactor (Nutritional Therapeutics). This product comes as tablets that are taken twice per day. For children, it should be ground up between two spoons into a coarse powder that can be added to several spoonfuls of applesauce. The NTFactor is not bitter, but it is slightly sour, and some children actually like the taste. The dose should be four to six tablets twice per day for adults. For children: one-half to one tablet for children up to two years-old; two tablets for children two to three years old; three to four tablets for children four to five years old; and four to five tablets for children five years old and older. Research has demonstrated no adverse responses with NTFactor, even at many times these doses. Since this formulation is a completely natural membrane lipid mixture, there are no known toxicities and no known toxic dose limits. NTFactor can also be taken in a form with vitamins, minerals, and probiotics (Propax). Lipid Replacement Therapy has been shown to improve fatigue scores and mitochondrial function in various chronic illnesses.[20]

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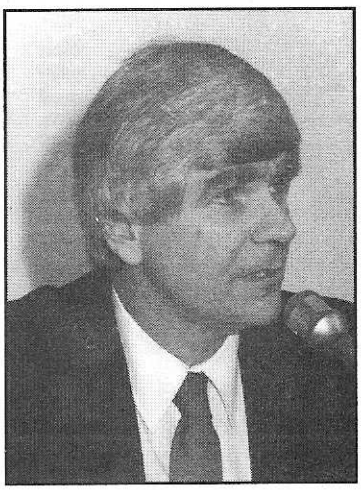

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