

ILADS

**DIAGNOSTIC HINTS AND TREATMENT
GUIDELINES
FOR LYME AND OTHER TICK BORNE ILLNESSES**

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INTRODUCTION

Welcome to the fourteenth edition of the "Guidelines." With the passage of time, our understanding of tick-borne illness has grown, so new information is presented to help us further refine our management techniques.

"Lyme Disease" is not simply an infection with *Borrelia burgdorferi*, but a complex illness potentially complicated by multiple tick-borne co-infections. In later stages, it also includes a very significant degree of immune suppression. This not only serves to perpetuate the infections, but it is probably responsible for the reactivation of latent infections, such as herpes-type viruses. Many collateral conditions result in those who have been chronically ill so it is not surprising that damage to virtually all bodily systems can result. To fully recover, all of these issues must be addressed in a thorough and systematic manner. No single treatment or medication will result in full recovery of the more ill patient. Only by addressing all these smaller issues and engineering treatments and solutions for all of them will we be able to restore full health to our patients.

Once again, the full spectrum of Lyme Borreliosis will be addressed, from the new bite, through early and late disseminated infections, and certainly to chronic Lyme Disease.

A very important issue is the definition of "Chronic Lyme Disease." Based on my clinical data and the latest published information, I offer the following definition. To be said to have chronic Lyme, these three criteria must be present:

1. Illness present for at least one year
2. Have persistent major neurologic involvement (such as encephalitis/encephalopathy, meningitis, etc.) or active arthritic manifestations (active synovitis).
3. Still have active infection with *B. burgdorferi*, regardless of prior antibiotic therapy (if any).

It is clear that in the great majority of patients, chronic Lyme is a disease affecting predominantly the nervous system. Thus, careful evaluation often includes neuropsychiatric testing, SPECT and MRI brain scans, CSF analysis when appropriate, regular input from Lyme-aware neurologists and psychiatrists, pain clinics, and occasionally specialists in psychopharmacology.

As an extension of the effect of chronic Lyme Disease on the central nervous system, new information has demonstrated a deleterious effect on the hypothalamic-pituitary axis. Varying degrees of pituitary insufficiency are being seen in these patients, the correction of which has resulted in restoration of energy, stamina and libido, and resolution of persistent hypotension. Unfortunately, not all specialists recognize pituitary insufficiency, partly because of the difficulty in making the laboratory diagnosis. However, the potential benefits of diagnosing and treating this justify the effort needed for full evaluation.

The concept of a “therapeutic alliance” between the caregiver and patient must again be emphasized. This means that the patient has to work with and become part of the medical team, and must take responsibility for complying with the recommendations given, maintaining the best possible health status, reporting promptly any problems or new symptoms, and especially in realizing that despite all our best efforts, success in diagnosis and treatment is never assured. The medical team must make great efforts to listen carefully to the patient and not be too quick to dismiss seemingly bizarre or illogical complaints.

I once again extend my best wishes to the many patients and caregivers who deal with Lyme, and a sincere thank you to my colleagues whose endless contributions have helped me shape my approach to tick borne illnesses. I hope that my new edition proves to be useful. Happy reading!

BACKGROUND INFORMATION

SPIROCHETE LOAD AND IMMUNE SUPPRESSION IN LYME DISEASE

The spirochete load has a direct bearing on the severity of Lyme presentation. Low spirochete loads result in mild or even inapparent infections that can be missed and remain present for years. As spirochete load increases, especially from subsequent tick bites, the morbidity of Lyme increases. Symptoms become apparent and more debilitating the larger the load, and testing for Lyme can become more accurate. Studies have shown that higher loads also begin to clinically impact the immune system, with invasion and killing of B- and T-lymphocytes, including Natural Killer Cells, and inhibition of lymphocyte transformation and mitogenesis. A corollary to the issue of spirochete load is the delicate balance between defense efficacy vs. pathogen strength. In other words, more severe illness also results from weakened defenses, such as from severe stress, immunosuppressant medications, and severe intercurrent illnesses.

The longer one is ill with Lyme, the more likely the illness will be more severe and treatment resistant. The same studies that demonstrated lymphocyte inhibition and lysis from high spirochete loads also demonstrated increased negative effects on the immune system the longer the spirochetes were present. We have seen this clinically, with the ultimate result being full blown Chronic Lyme Disease.

CO-INFECTION

A huge body of research and clinical experience has demonstrated the nearly universal phenomenon in Lyme patients of co-infection with multiple tick-borne pathogens. Significant numbers of Lyme patients have been shown to also carry Babesia species, Ehrlichias, Anaplasmas, Mycoplasmas, Bartonellas and viruses. Rarely, yeast forms have been seen in peripheral blood. Studies have shown that co-infection results in a more severe clinical presentation, with more organ damage, and the pathogens become more difficult to eradicate. It is known that Babesia infection, like Lyme Borreliosis, is immunosuppressive. There are changes in the clinical presentation compared to when each infection is present individually, with different symptoms, and atypical signs. There may be decreased reliability of standard diagnostic tests, and most importantly, there is recognition that chronic, persistent forms of each of these infections do indeed exist. As time goes by, I am convinced that even more pathogens will be found.

Therefore, real, clinical Lyme as we have come to know it, especially the later and more severe presentations, probably represents a mixed infection. I will leave to the reader the implications of how this may explain the discrepancy between laboratory study of pure Borrelia infections, and what front-line physicians have been seeing for years in real patients.

The evaluation of a Lyme patient must begin with testing for all currently known tick borne pathogens. Serological studies for Borrelia, Babesia Bartonella and Ehrlichia should be combined where appropriate with direct antigen assays. Antigen detection tests (antigen capture and PCR) are especially helpful in evaluating the seronegative patient and those still ill or relapsing after therapy. Unfortunately, over a dozen protozoans other than Babesia microti can be found in ticks, yet commercial tests for only B. microti and WA-1 are available at this time, so as in Borrelia, clinical assessment is the primary diagnostic tool. In Ehrlichiosis, test for both the monocytic and granulocytic forms. Many presently uncharacterized Ehrlichia-like organisms can be found in ticks and may not be picked up by currently available assays, so in this illness too, serologies are only an adjunct in making the diagnosis.

Babesia are parasites, and I suggest that if a coinfection is found involving this organism, treat this first, so that subsequent therapy for the other pathogens will be more effective.

COLLATERAL CONDITIONS

Experience has shown that collateral conditions exist in those who have been ill a long time. The evaluation should include testing both for differential diagnosis and for uncovering other subtle abnormalities that may coexist.

Test B12 levels, and be prepared to aggressively treat with parenteral formulations.

Pituitary and other endocrine abnormalities are far more common than generally realized. Evaluate fully, including growth hormone levels. When testing the thyroid, measure free T3 and free T4 levels and TSH. Nuclear scanning and testing for autoantibodies may be necessary.

Activation of the inflammatory cascade has been implicated in blockade of cellular hormone receptors. One example of this is insulin resistance, which may partly account for the dyslipidemia and weight gain that is noted in 80% of chronic Lyme patients. Clinical hypothyroidism can result from receptor blockade and thus hypothyroidism can exist despite normal serum hormone levels. In addition to measuring free T3 and T4 levels, check basal A.M. body temperatures. If hypothyroidism is found, you may need to treat with both T3 and T4 preparations until blood levels of both are normalized.

Tilt table testing is another powerful tool which, just as in CFIDS, may demonstrate neurally mediated hypotension (NMH). NMH can result from autonomic neuropathy and endocrine dyscrasias. If NMH is present, treatment can dramatically lessen fatigue, palpitations and wooziness, and increase stamina. This test should be done by a cardiologist and include Isuprel challenge. This will demonstrate not only if NMH is present, but also the relative contributions of hypovolemia and sympathetic dysfunction. Therapy is based on blood volume expansion (increased sodium and fluid intake and possibly Florinef plus potassium). If not sufficient, beta blockade may be added based on response to the Isuprel challenge.

Magnesium deficiency is very often present and quite severe. Hyperreflexia, muscle twitches, myocardial irritability, poor stamina and recurrent tight muscle spasms are clues to this deficiency. Magnesium is predominantly an intracellular ion, so blood level testing is of little value. Oral preparations are acceptable for maintenance, but most need additional, parenteral dosing: 1 gram IV or IM at least once a week until neuromuscular irritability has cleared.

SPECT scanning of the brain, if done by knowledgeable radiologists using high resolution equipment, will show characteristic abnormalities in Lyme encephalopathy. What these scans demonstrate is cerebral vasculitis, which is the underlying mechanism for much of the symptoms of Lyme. This not only helps with the differential diagnosis, but if done before and after acetazolamide, it will guide in the use of vasodilators, which may clear some cognitive symptoms. Therapy can include acetazolamide, serotonin agonists and even Ginkgo biloba. Therapeutic trials of these may be needed.

Two different researchers have provided evidence that *B. burgdorferi*, like many other pathogenic bacteria, can produce neurotoxins. Early clinical trials aimed at removing these toxins have proven quite promising. I will discuss this in more detail in a later section.

LYME BORRELIOSIS

DIAGNOSTIC HINTS

Lyme is diagnosed clinically, as no currently available test, no matter the source or type, is definitive in ruling in or ruling out infection with these pathogens, or whether these infections are responsible for the patient's symptoms. The entire clinical picture must be taken into account, including a search for concurrent conditions and alternate diagnoses, and other reasons for some of the presenting complaints. Often, much of the diagnostic process in late, disseminated Lyme involves ruling out other illnesses and defining the extent of damage that might require separate evaluation and treatment.

Consideration should be given to tick exposure, rashes (even atypical ones), evolution of typical symptoms in a previously asymptomatic individual, and results of tests for tick-borne pathogens. Another very important factor is response to treatment — presence or absence of Jarisch Herxheimer-like reactions, the classic four-week cycle of waxing and waning of symptoms, and improvement with therapy.

ERYTHEMA MIGRANS

Erythema migrans (EM) is diagnostic of *Bb* infection, but is present in fewer than half. Even if present, it may go unnoticed by the patient. It is an erythematous, centrifugally expanding lesion that is raised and warm. Sometimes there is mild stinging or pruritus. The EM rash will begin four days to several weeks after the bite, and may be associated with constitutional symptoms. Multiple lesions are present less than 10% of the time, but do represent disseminated disease. Some lesions have an atypical appearance and skin biopsy specimens may be helpful. When an ulcerated or vesicular center is seen, this may represent a mixed infection, involving other organisms besides *B. burgdorferi*.

After a tick bite, serologic tests (ELISA, IFA, western blots, etc.) are not expected to become positive until several weeks have passed. Therefore, if EM is present, treatment must begin immediately, and one should not wait for results of *Borrelia* tests. You should not miss the chance to treat early disease, for this is when the success rate is the highest. Indeed, many knowledgeable clinicians will not even order a *Borrelia* test in this circumstance.

DIAGNOSING LATER DISEASE

When reactive, serologies indicate exposure only and do not directly indicate whether the spirochete is now currently present. Because *Bb* serologies often give inconsistent results, test at more than one laboratory using, if possible, different methods. The suggestion that two-tiered testing, utilizing an ELISA as a screening tool, followed, if positive, by a confirmatory western blot, is illogical in this illness. The ELISA is not sensitive enough to serve as an adequate screen, and there are many patients with Lyme who test negative by ELISA yet have fully diagnostic western blots. I therefore recommend against using the ELISA. Order IgM and IgG western blots — but be aware that in late disease there may be repeatedly peaking IgM's and therefore a reactive IgM may not differentiate early from late disease, but it does suggest an active infection. When late cases of LB are seronegative, 36% will transiently become seropositive at the completion of successful therapy.

Western blots are reported by showing which bands are reactive. 41KD bands appear the earliest but can cross react with other spirochetes. The 18KD, 23–25KD (Osp C), 31KD (Osp A), 34KD (Osp B), 37KD, 39KD, 83KD and the 93KD bands are the most specific but appear later or may not appear at all. You need to see at least the 41KD and one of the specific bands. 55KD, 60KD, 66KD, and 73KD are nonspecific and nondiagnostic.

PCR tests are now available, and although they are very specific, sensitivity remains poor, possibly less than 30%. This is because Bb causes a deep tissue infection and is only transiently found in body humors. Therefore, just as in routine blood culturing, multiple specimens must be collected to increase yield; a negative result does not rule out infection, but a positive one is significant. You can test whole blood, buffy coat, serum, urine, spinal and other body fluids, and tissue biopsies. Several blood PCRs can be done, or you can run PCRs on whole blood, serum and urine simultaneously at a time of active symptoms. The patient should be antibiotic free for at least six weeks before testing to obtain the highest yield.

Antigen capture is becoming more widely available, and can be done on urine, CSF, and synovial fluid.

Sensitivity is still low, but specificity is high.

Spinal taps are not routinely recommended, as a negative tap does not rule out Lyme. Antibodies to Bb most commonly are found in Lyme meningitis, but are rarely seen in non-meningitic CNS infection, including even advanced encephalopathy. Even in meningitis, antibodies are detected in the CSF in less than 20% of patients with late disease. Therefore, spinal taps are only performed on patients with pronounced neurological manifestations in whom the diagnosis is uncertain, if they are seronegative, or are still significantly symptomatic after completion of treatment. When done, the goal is to rule out other conditions, and to determine if Bb antigens or nucleic acids are present. It is especially important to look for elevated protein and mononuclear cells, which would dictate the need for more aggressive therapy, as well as the opening pressure, which can be elevated and add to headaches, especially in children.

I strongly urge you to biopsy all unexplained skin lesions/rashes and perform PCR and careful histology. You will need to alert the pathologist to look for spirochetes.

DIAGNOSTIC CHECKLIST

To aid the clinician, a workable set of diagnostic criteria was developed with the input of dozens of front line physicians. The resultant document has proven to be extremely useful not only to the clinician, but it also can help clarify the diagnosis for third party payers and utilization review committees. **It is important to note that the CDC's published reporting criteria are for surveillance only, not for diagnosis.**

LYME BORRELIOSIS DIAGNOSTIC CRITERIA	RELATIVE VALUE
	1
Tick exposure in an endemic region	2
Historical facts and evolution of symptoms consistent with Lyme	
Systemic signs & symptoms consistent with Bb infection (other potential diagnoses excluded):	
Single system, e.g., monoarthritis	1
Two or more systems, e.g., monoarthritis and facial palsy	2
Erythema migrans, physician confirmed	7
Acrodermatitis Chronica Atrophicans, biopsy confirmed	7
Seropositivity	3
Seroconversion on paired sera	4
Tissue microscopy, silver stain	3
Tissue microscopy, monoclonal immunofluorescence	4
Culture positivity	4

B. burgdorferi antigen recovery	4
B. burgdorferi DNA/RNA recovery	4

DIAGNOSIS

Lyme Borreliosis Highly Likely	7 or above
Lyme Borreliosis Possible	5–6
Lyme Borreliosis Unlikely	4 or below

I suggest that when using these criteria, you state Lyme Borreliosis is “unlikely,” “possible,” or “highly likely” based upon the following criteria—then list the criteria.

LYME DISEASE TREATMENT GUIDELINES

LYME BORRELIOSIS

GENERAL INFORMATION

After a tick bite, Bb undergoes rapid hematogenous dissemination, and, for example, can be found within the central nervous system as soon as twelve hours after entering the bloodstream. This is why even early infections require full dose antibiotic therapy with an agent able to penetrate all tissues in concentrations known to be bactericidal to the organism.

It has been shown that the longer a patient had been ill with Bb prior to first definitive therapy, the longer the duration of treatment must be, and the need for more aggressive treatment increases.

More evidence has accumulated indicating the severe detrimental effects of immunosuppressants including steroids in the patient with active B. burgdorferi infection. Never give steroids or any other immunosuppressant to any patient who may even remotely be suffering from Lyme, or serious, permanent damage may result, especially if given for anything greater than a short course. If immunosuppressive therapy is absolutely necessary, then potent antibiotic treatment should begin at least 48 hours prior to the immunosuppressants.

TREATMENT RESISTANCE

Bb contains beta lactamases, which, with some strains, may confer resistance to cephalosporins and penicillins. This is apparently a slowly acting enzyme system, and may be overcome by higher or more continuous drug levels especially when maintained by continuous infusions (cefotaxime) and by depot preparations (benzathine penicillin). Nevertheless, some penicillin and cephalosporin treatment failures do occur and have responded to sulbactam/ampicillin, imipenim, and vancomycin, which act through different cell wall mechanisms than penicillin and the cephalosporins.

There is evidence that B. burgdorferi can remain viable within cells, such as macrophages, lymphocytes, endothelial cells, neurons, and fibroblasts. Bb has been shown to evade the effects of beta lactam antibiotics in vitro by sequestering in these intracellular niches. In addition, Bb can coat itself with host cell membranes, and it secretes a glycoprotein that can encapsulate the organism (an “S-layer”). Because this glycoprotein binds host IgM, it is possible that host protein as well as cell membrane hide Borrelial antigens. In theory at least, these coatings interfere with immune recognition, thus affecting the clearing of Bb, and also cause seronegativity.

There are multiple strains of *Borrelia burgdorferi* and they vary in their antigen profile and antibiotic susceptibilities. It has also been recognized that *B. burgdorferi* can exist in at least three different morphologic forms: spirochetal, spheroplast (or l-form), and the recently discovered cystic form.

L-forms and cystic forms do not contain cell walls, and thus beta lactam antibiotics will not affect them. Spheroplasts seem to be susceptible to tetracyclines and some erythromycins, yet the cyst has so far only been proven to be susceptible to metronidazole. Apparently, Bb can shift among the three forms during the course of the infection and cause the varying serologic responses seen over time, including seronegativity. Because of this, it may be necessary to change antibiotic or even prescribe a combination of agents.

Vegetative endocarditis has been associated with *Borrelia burgdorferi*, but the vegetations may be too small to detect with echocardiography. Keep this in mind when evaluating patients with murmurs, as this may explain why some patients seem to continually relapse after even long courses of antibiotics.

COURSE DURING THERAPY

As the spirochete has a very long generation time (12 to 24 hours in vitro and possibly much longer in living systems) and may have periods of dormancy, during which time antibiotics will not kill the organism, treatment has to be continued for a long period of time to eradicate all the active symptoms and prevent a relapse, especially in late infections. If treatment is discontinued before all symptoms of active infection have cleared, the patient will remain ill and possibly relapse further. In general, early disseminated LB is treated for four to six weeks, and late LB usually requires a minimum of four to six months of continuous treatment. All patients respond differently and therapy must be individualized. It is not uncommon for a patient who has been ill for many years to require open ended treatment regimens; indeed, some patients will require ongoing maintenance therapy to remain well.

Several days after the onset of appropriate antibiotic therapy, symptoms often flare due to lysis of the spirochetes with release of increased amount of antigenic material and possibly bacterial toxins. This is referred to as a Jarish Herxheimer-like reaction. Because it takes 48 to 72 hours of therapy to initiate bacterial killing, the Herxheimer reaction is therefore delayed. This is unlike syphilis, in which these reactions can occur within hours.

It has been observed that symptoms will flare in cycles every four weeks. It is thought that this reflects the organism's cell cycle, with the growth phase occurring once per month (intermittent growth is common in *Borrelia* species). As antibiotics will only kill bacteria during their growth phase, therapy is designed to bracket at least one whole generation cycle. This is why the minimum treatment duration should be at least four weeks. If the antibiotics are working, over time these flares will lessen in severity and duration. The very occurrence of ongoing monthly cycles indicates that living organisms are still present and that antibiotics should be continued.

With treatment, these monthly symptom flares are exaggerated and presumably represent recurrent Herxheimer-like reactions as Bb enters its vulnerable growth phase then are lysed. For unknown reasons, the worst occurs at the fourth week of treatment. Observation suggest that the more severe this reaction, the higher the germ load, and the more ill the patient. In those with long-standing highly symptomatic disease who are on IV therapy, the week-four flare can be very severe, similar to a serum sickness reaction, and be associated with transient leucopenia and/or elevations in liver enzymes. If this happens, decrease the dose temporarily, or interrupt treatment for several days, then resume with a lower dose. If you are able to continue or resume therapy, then patients continue to improve. Those whose treatment is stopped and not restarted at this point usually will need retreatment in the future due to ongoing or recurrent symptoms because the infection was not eradicated. Patients on IV therapy who have a strong reaction at the fourth week will need to continue parenteral antibiotics for several months, for when this monthly reaction finally lessens in severity, then oral or IM medications can be substituted. Indeed, it is just this observation that guides the clinician in determining the endpoint of IV treatment. In general, IV therapy is given until there is a clear positive response, then treatment is changed to IM or po until free of signs of active infection for

4 to 8 weeks. Some patients, however, will not respond to IM or po treatment and IV therapy will have to be used throughout. As mentioned earlier, leucopenia may be a sign of persistent Ehrlichiosis, so be sure to look into this.

Repeated treatment failures should alert the clinician to the possibility of an otherwise inapparent immune deficiency, and a workup for this may be advised. Obviously, evaluation for co-infection should be performed, and a search for other or concurrent diagnoses needs to be entertained.

There are three things that will predict treatment failure regardless of which regimen is chosen: Non-compliance, alcohol use on a regular basis, and failure of the patient to obtain proper rest. Advise them to take a break when (or ideally before) the inevitable mid afternoon fatigue sets in.

All patients must keep a carefully detailed daily diary of their symptoms to help us judge the effects of treatment, the presence of the classic four week cycle, and treatment endpoint. One must follow such diaries, temperature readings in late afternoon, physical findings, notes from physical therapists, and cognitive testing to best judge when to change or end antibiotics.

Remember — there currently is no test for cure, so this clinical follow-up assumes a major role in Lyme Disease care.

BORRELIA NEUROTOXIN (With thanks to Dr. Shoemaker)

Two groups have reported evidence that Borrelia, like several other bacteria, produce neurotoxins. These compounds reportedly can cause many of the symptoms of encephalopathy, cause an ongoing inflammatory reaction manifested as some of the virus-like symptoms common in late Lyme, and also potentially interfere with hormone action by blocking hormone receptors. At this time, there is no assay available to detect whether this compound is present, nor can the amount of toxin be quantified. Indirect measures are currently employed, such as measures of cytokine activation and hormone resistance. A visual contrast sensitivity test (VCS test) reportedly is quite useful in documenting CNS effects of the neurotoxin, and to follow effects of treatment. This test is available at some centers and on the internet.

It has been said that the longer one is ill with Lyme, the more neurotoxin is present in the body. It probably is stored in fatty tissues, and once present, persists for a very long time. This may be because of enterohepatic circulation, where the toxin is excreted via the bile into the intestinal tract, but then is reabsorbed from the intestinal tract back into the blood stream. This forms the basis for treatment.

Synthetic fiber agents, available by prescription for the treatment of high cholesterol, have the ability to bind some bacterial toxins. When take orally in generous amounts, the neurotoxin, present in the intestinal tract, binds to the resin, is trapped, and then excreted. Thus, over several weeks, the level of neurotoxin is depleted and clinical improvement can be seen. Current experience is that improvement is first seen in three weeks, and treatment continues for two to four months. Retreatment is always possible.

Two prescription medications that can bind these toxins include cholestyramine resin (Questran), and Welchol pills. These medications may bind not only toxins but also many drugs and vitamin supplements. Therefore no other oral medications or supplements should be taken from one hour before, to three hours after a dose of one of these fiber agents.

Cholestyramine must be taken four times daily, and Welchol is prescribed at three pills twice daily. While the latter is obviously much simpler to use, it is less effective than cholestyramine. The main side effects are bloating and constipation, best handled with increased fluid intake and gentle laxatives.

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LYME DISEASE TREATMENT INFORMATION

There is no universally effective antibiotic for treating LB. The choice of medication used and the dosage prescribed will vary for different people based on multiple factors. These include duration and severity of illness, presence of co-infections, immune deficiencies, prior significant immunosuppressant use while infected, age, weight, gastrointestinal function, blood levels achieved, and patient tolerance. Doses found to be effective clinically are often higher than those recommended in older texts. This is due to deep tissue penetration by Bb, its presence in the CNS including the eye, within cells, within tendons, and because very few of the many strains of this organism now known to exist have been studied for antibiotic susceptibility. In addition, all animal studies of susceptibility to date have only addressed early disease in models that behave differently than human hosts. Therefore, begin with a regimen appropriate to the setting, and if necessary, modify it over time based upon response.

ANTIBIOTICS

There are several types of antibiotics in general use for Bb treatment. The tetracyclines, including doxycycline and minocycline, are bacteriostatic unless given in high doses. If high blood levels are not attained, treatment failures in early and late disease are common. However, these high doses can be difficult to tolerate. For example, doxycycline can be very effective but only if adequate blood levels are achieved either by high oral doses (300 to 600 mg daily) or by parenteral administration.

Penicillins are bactericidal. As would be expected in managing an infection with a gram negative organism such as Bb, amoxicillin has been shown to be more effective than oral penicillin V. Because of its short half-life and need for high levels, amoxicillin is usually administered along with probenecid. Since blood levels are extremely variable they should be measured.

Cephalosporins must be of advanced generation: first generation drugs are rarely effective, and second generation drugs are comparable to amoxicillin and doxycycline both in-vitro and in-vivo. Third generation agents are currently the most effective of the cephalosporins because of their very low MBC's (0.06 for ceftriaxone) and they have been shown to be effective in penicillin and tetracycline failures. Cefuroxime axetil (Ceftin), a second generation agent, is also effective against staph and thus is useful in treating atypical erythema migrans that may represent a mixed infection, containing some of the more common skin pathogens in addition to Bb.

When choosing a third generation cephalosporin, there are several points to remember: Ceftriaxone has 95% biliary excretion and can crystallize in the biliary tree with resultant colic and possible cholecystitis. GI excretion results in a large impact on gut flora. Biliary and superinfection problems with ceftriaxone can be lessened if this drug is given in interrupted courses, such as three to five days in a row each week. More recently, chenodeoxycholic acid, used to dissolve gallstones, is being prescribed along with ceftriaxone as prophylaxis. Cefotaxime is less convenient to administer because of the need for either multiple daily doses or continuous infusions, but as it has only 5% biliary excretion, it never causes biliary concretions, and may have less impact on gut flora. It is the experience of some clinicians that cefotaxime can be even more efficacious if given as a continuous infusion, rather than in interrupted doses.

Erythromycin has been shown to be almost ineffective as monotherapy. The advanced macrolides and azalides such as azithromycin and clarithromycin can be difficult to tolerate orally due to their tendency to promote yeast overgrowth and poor GI tolerance at the high doses needed. As they have impressively low MBCs and do concentrate in tissues and penetrate cells, they theoretically should be ideal agents. However, initial clinical results were disappointing, especially with oral azithromycin. It has been suggested that when Bb is within a cell, it is held within a vacuole and bathed in fluid of low pH, and this acidity may inactivate this class of antibiotics. Therefore, they are administered concurrently with hydroxychloroquine or amantadine, which raise vacuolar pH, rendering these antibiotics more effective. It is not known whether this same technique will make erythromycin a more effective antibiotic in LB. Another alternative is to

administer azithromycin parenterally. Results are excellent, but expect to see abrupt Jarisch-Herxheimer reactions.

Metronidazole (Flagyl) is commonly used in select patients with treatment resistant, chronic Lyme. When present in a hostile environment, such as growth medium lacking some nutrients, or spinal fluid, or serum with certain antibiotics added, Bb will change into a cystic form. This cyst seems to be able to remain dormant, but when placed into an environment more favorable to its growth, the cyst can open, and an intact spirochete emerges. The conventional antibiotics used for Lyme, such as the penicillins, cephalosporins, etc. do not kill the cystic form of Bb. Furthermore, the cyst lacks the usual surface antigens found on the spirochete (these are the markers detected by ELISAs and western blots). This may be another reason for the chronically sick Lyme patient remaining seronegative.

There is evidence that metronidazole will kill the cystic form. This fits with the now well known clinical observations that metronidazole can be remarkably effective for many chronic Lyme patients. However, this medication apparently has no effect on intact spirochetes. Therefore, the trend now is to treat the chronically infected patient who has resistant disease by combining metronidazole with one or two other antibiotics to target all forms of Bb. Because there is laboratory evidence that tetracyclines may inhibit the effect of metronidazole, this class of medication may not be as useful as others in these two- and three-drug regimens. There have been some recent reports that Bb does not contain genes that would confer susceptibility to metronidazole. However, this clearly does not fit with in vitro and a large body of clinical data, which have demonstrated the usefulness of this agent in the Lyme patient. Perhaps we do not have all the genetic information needed to dismiss the use of this agent. Once again, real world experience is one step ahead of bench research.

Important precautions:

1. Pregnancy while on metronidazole is not advised, as there is a risk of birth defects.
2. No alcohol consumption! A severe, "antabuse" reaction will occur, consisting of severe nausea, flushing, headache, and other unpleasant symptoms.
3. Metronidazole is potentially neurotoxic. Peripheral neuropathy may result. Therefore, breaks in treatment are commonly prescribed, such as using this agent every other week.
4. Yeast overgrowth is especially common. A strict anti-yeast regimen must be followed.
5. VERY severe Herxheimer-like reactions are seen in the more ill patient during the first week of therapy, and again four weeks later.

COMBINATION THERAPY

This consists of using two or more dissimilar antibiotics simultaneously. There are several reasons for this. Combinations should utilize dissimilar antibiotics for antibiotic synergism, to better compensate for differing killing profiles and sites of action of the individual medications, and to cover the three known morphologic forms of Bb. The idea is to work in body fluids and in deep tissues, outside and within cells, and effect killing by different mechanisms for synergism. An example is a combination of amoxicillin and clarithromycin. Note how complimentary these two are for treating infection with Bb. GI intolerance and yeast superinfections are the biggest drawbacks to this type of treatment. However, these complications can often be prevented or easily treated, and the clinically observed benefits of this type of regimen clearly have outweighed these problems in selected patients.

PULSE THERAPY

This consists of administering antibiotics (usually parenteral ones) two to three days in a row per week. The efficacy of this regimen is based on the fact that it takes 48 to 72 hours of continuous bactericidal antibiotic levels to kill the spirochete, yet it will take longer than the four to five days between pulses for the spirochetes to recover. This allows for several advantages:

- Dosages are doubled (ie: cefotaxime, 12 g daily), increasing efficacy
- More toxic medications can be used with increased safety (ie: vancomycin)
- May be effective when conventional, daily regimens have failed.
- IV access may be easier or more tolerable
- More agreeable lifestyle for the patient
- Often less costly than daily regimens

Note that this type of treatment is expected to continue for a minimum of ten weeks, and often must continue beyond twenty weeks. As with all Lyme treatments, specific dosing and scheduling must be tailored to the individual patient's clinical picture based upon the treating physician's best clinical judgment.

MONITORING THERAPY

Drug levels are measured, where possible, to confirm adequate dosing. The regimen may have to be modified to optimize the dose, and again at any time major changes in the treatment regimen occur. With parenteral therapy, CBC and chem/liver panels are done at least twice each month, especially during symptom flares, with urinalysis and protime monitored monthly.

INDICATORS FOR PARENTERAL THERAPY

The following are guidelines only and are not meant to be absolute. It is based on retrospective study of over 600 patients with late Lyme disease.

- Illness for greater than one year
- Prior immunosuppressive therapy
- Major neurological involvement
- Active synovitis with high sedimentation rate
- Elevated protein or cells in the CSF

ANTIBIOTIC CHOICES

ORAL THERAPY

Always check blood levels when using agents marked with an *, and adjust dose to achieve a peak level in the mid- teens and a trough greater than five. Because of this, the doses listed below may have to be raised. Consider Doxycycline first due to concern for Ehrlichia.

*Amoxicillin	Adults: 1g q8h plus probenecid 500mg q8h; doses up to 6 grams daily are often needed Pregnancy: 1g q6h and adjust Children: 50 mg/kg/day divided into q8h doses
*Doxycycline	Adults: 100 mg qid with food; doses of up to 600 mg daily are often needed, as doxycycline is only effective at high blood levels. Not for children or in pregnancy. If levels are too low at tolerated doses, give parenterally.
*Cefuroxime axetil	Oral alternative that may be effective in amoxicillin and doxycycline failures. Useful in EM rashes co-infected with common skin pathogens.

	Adults and pregnancy: 1g q12h and adjust. Children: 125 to 500 mg q12h based on weight.
Tetracycline	Adults only, and not in pregnancy. 500 mg tid to qid
Erythromycin	Poor response and not recommended.
Clarithromycin	Adults: 500 to 1000 mg q12h. Add hydroxychloroquine, 200–400 mg/d or amantadine 100–200 mg/d.
Azithromycin	Cannot be used in pregnancy or in younger children Adults: 500 to 1200 mg/d. Adolescents: 250 to 500 mg/d. Add hydroxychloroquine, 200–400 mg/d, or amantadine 100–200 mg/d Cannot be used in pregnancy. Oral azithromycin is not as effective as clarithromycin.
Augmentin	Cannot exceed three tablets daily due to the clavulanate, thus is given with amoxicillin. This combination can be effective when Bb beta lactamase is felt to be present.
Chloramphenicol	Not recommended as not proven and potentially toxic.
Metronidazole (see text)	500 to 1500 mg daily in divided doses. Adults only.

PARENTERAL THERAPY

Ceftriaxone	Risk of biliary sludging can be minimized with intermittent breaks in therapy (ie: infuse five or less days in a row per week). Adults and pregnancy: 2g q12h, four days in a row each week. Children: 75 mg/kg/day up to 2g/day
Cefotaxime	Comparable efficacy to ceftriaxone; no biliary complications. Adults and pregnancy: 2g q8h; may dose as high as 12g daily. Suggest a continuous infusion. Children: 90 to 180 mg/kg/day dosed q6h (preferred) or q8h, not to exceed 12 g daily.
*Doxycycline	Requires central line as is caustic. Surprisingly effective, probably because higher overall, and spiked blood levels when given parenterally. Always measure blood levels. Adults: 400 mg q24h and adjust based on levels. Cannot be used in pregnancy or in younger children.
Azithromycin	Requires central line as is caustic. Dose: 500 to 1000 mg daily in adolescents and adults.
Penicillin G	IV penicillin G is minimally effective and not

	recommended.
Benzathine penicillin	Surprisingly effective IM alternative to oral therapy. May need to begin at lower doses as strong, prolonged (6 or more week) Herxheimer-like reactions have been observed. Adults: 1.2 million U three times per week (higher doses with large body habitus) Adolescents: 300,000 to 2.4 million U weekly. May be used in pregnancy.
	Poorly studied but anecdotally effective
Vancomycin	Observed to be one of the best drugs in treating Lyme, but potential toxicity limits its use. It is a perfect candidate for pulse therapy to minimize these concerns. Use standard doses and confirm levels.
Imipenim and Unisyn	Similar in efficacy to cefotaxime, but often works when cephalosporins have failed. Must be given q6 to q8 hours.
Cefuroxime	Useful but not demonstrably better than ceftriaxone or cefotaxime.
Ampicillin IV	More effective than penicillin G. Must be given q6 hours.

TREATMENT CATEGORIES

PROPHYLAXIS of high risk groups — education and preventive measures. Antibiotics are not given.

TICK BITES — Embedded Deer Tick With No Signs or Symptoms of Lyme (see appendix)

Decide to treat based on the type of tick, whether it came from an endemic area and percent infected, how it was removed, and length of attachment (nymphs: at least one day; adults: anecdotally, as little as four hours). The risk of transmission is greater if the tick is engorged, or of it was removed improperly allowing the tick's contents to spill into the bite wound. High risk bites are treated as follows (remember the possibility of coinfection!):

1. Adults: Oral therapy for 21 days.
2. Pregnancy: Amoxicillin 1000 mg q6h for 6 weeks. Test for Babesia, Bartonella and Ehrlichia.
Alternative: Cefuroxime axetil 1000 mg q12h for 6 weeks.
3. Young Children: Oral therapy for 21 days.

EARLY LOCALIZED — Single erythema migrans with no constitutional symptoms:

1. Adults: oral therapy for 6 weeks.
2. Pregnancy: 1st and 2nd trimesters: IV X 21 days then oral X 6 weeks
3rd trimester: Oral therapy X 6 weeks.
Any trimester — test for Babesia, Bartonella, and Ehrlichia
3. Children: oral therapy for 6 weeks.

DISSEMINATED DISEASE — Multiple lesions, constitutional symptoms, lymphadenopathy, or any other manifestations of dissemination.

EARLY DISSEMINATED — Milder symptoms present for less than one year and not complicated by immune deficiency or prior immunosuppressive treatment:

1. Adults: Oral therapy until no active disease for 4 weeks (4–6 months typical)
2. Pregnancy: As in localized disease, but duration as above. Treat throughout pregnancy, and do not breast feed.
3. Children: Oral therapy with duration based upon clinical response.

PARENTERAL ALTERNATIVES for more ill patients and those unresponsive to or intolerant of oral medications:

1. Adults and children: IV therapy for at least 6 weeks (until clearly improved). Follow with oral therapy or IM benzathine penicillin until no active disease for 6–8 weeks. IV may have to be resumed if oral or IM therapy fails.
2. Pregnancy: IV then oral therapy as above.

LATE DISSEMINATED — Present greater than one year, more severely ill patients, and those with prior significant steroid therapy or any other cause of impaired immunity:

1. Adults and pregnancy: Extended IV therapy (10 or more weeks), then oral or IM, if effective, to same endpoint.
2. Children: IV therapy for 6 or more weeks, then oral or IM follow up as above.

CHRONIC LYME DISEASE

By definition, this category consists of patients with active infection, of a more prolonged duration, and most likely have higher spirochete loads, weaker defense mechanisms, possibly more virulent or resistant strains, and probably are significantly co-infected. Neurotoxins may also be significant in these patients. Search for and treat concurrent illnesses including viruses, chlamydias, and mycoplasmas. These patients require a full evaluation for all of these problems, and each abnormality must be addressed.

This group will most likely need parenteral therapy, especially high dose, pulsed therapy, and antibiotic combinations, including metronidazole. Antibiotic therapy will need to continue for many months, and the antibiotics may have to be changed periodically to break plateaus in recovery. Be vigilant for treatment-related problems such as antibiotic-associated colitis, yeast overgrowth, intravenous catheter complications, and abnormalities in blood counts and chemistries.

If treatment can be continued long term, then a remarkable degree of recovery is possible. However, attention must be paid to all treatment modalities for such a recovery — not only antibiotics, but rehab programs, nutritional supplements, enforced rest, low carbohydrate, high fiber diets, attention to food sensitivities, avoidance of stress, abstinence from caffeine and alcohol, and absolutely no immunosuppressants, even local doses of steroids (intra articular injections, for example).

Unfortunately, not all patients with chronic Lyme disease will fully recover and treatment may not eradicate the active *Borrelia* infection. Such individuals may have to be maintained on open-ended, ongoing antibiotic therapy, for they repeatedly relapse after antibiotics are stopped. Maintenance antibiotic therapy is thus mandatory.

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SAFETY

Nearly two decades of experience in treating thousands of patients with Lyme has proven that therapy as described above, although intense, is generally well tolerated. The most common adverse reaction seen is allergy to probenecid. In addition, yeast superinfections are seen, but these are generally easily recognized and managed. The induction of *Clostridium difficile* toxin production is seen most commonly with ceftriaxone, but can occur with any of the antibiotic regimens mentioned in this document. However, pulsed dose therapy and regular use of the lactobacillus preparations seems to be helpful in controlling yeast and antibiotic related colitis, as the number of cases of *C. difficile* in Lyme patients is low when these guidelines are followed.

When using central intravenous lines including PICC lines (peripherally inserted central catheters), if ANY line problems arise, it is recommended that the line be pulled for patient safety. Salvage attempts (urokinase, repairing holes) are often ineffective and may not be safe.

Please advise all patients who take the tetracyclines of skin and eye sensitivity to sunlight and the proper precautions, and advise birth control if appropriate. When doxycycline is given parenterally, do not refreeze the solution prior to use!

Remember, years of experience with chronic antibiotic therapy in other conditions, including rheumatic fever, acne, gingivitis, recurrent otitis, recurrent cystitis, COPD, bronchiectasis, and others have not revealed any consistent dire consequences as a result of such medication use. Indeed, the very real consequences of untreated, chronic persistent infection by *B. burgdorferi* can be far worse than the potential consequences of this treatment.

CO-INFECTIONS IN LYME

PIROPLASMOSIS (Babesiosis)

GENERAL INFORMATION

Piroplasmids are not bacteria, they are protozoans. Therefore, they will not be eradicated by any of the currently used Lyme treatment regimens. Therein lies the significance of co-infections — if a Lyme patient has been extensively treated yet is still ill, suspect a co-infection.

Babesia infection is becoming more commonly recognized, especially in patients who already have Lyme Disease. It has been published that as many as 66% of Lyme patients show evidence of co-infection with Babesia. It has also been reported that Babesial infections can range in severity from mild, subclinical infection, to fulminant, potentially life-threatening illness. The more severe presentations are more likely to be seen in immunocompromised and elderly patients. Milder infections are often missed because the symptoms are incorrectly ascribed to Lyme. Babesial infections, even mild ones, may recrudesce and cause severe illness. This phenomenon has been reported to occur at any time, even up to several years after the initial infection. Furthermore, asymptomatic carriers pose risks: to the blood supply as this infection has been reported to be passed on by blood transfusion, and to the unborn child from an infected mother as it can be transmitted *in utero*. Some quotes from the literature:

Krause, PJ, Spielman, A, Telford, SR et.al. *Persistent parasitemia after acute Babesiosis* N Engl J Med 1998. 339:160

“The clinical spectrum of human Babesiosis ranges from an apparently silent infection to a fulminant malaria-like disease.”

“When left untreated, silent Babesial infection may persist for months to years.”

“Silent infections, which occur in about a third of infected people, may recrudesce.”

“Babesial infection may recrudesce after many months of asymptomatic parasitemia.”

“Although parasites were initially detected microscopically in the blood of two of the untreated subjects, and all of the treated subjects, none could be found a week after the onset of illness.”

“Persistent symptoms of Babesiosis accompanied persistent blood-borne Babesial DNA.”
“The persistence of seroreactivity increasingly correlated with the persistence of Babesial DNA.”
“In those with only subtle symptoms, Babesiosis often remains undiagnosed.”
“Furthermore, physicians tend not to recognize Babesial infection in those who are co-infected with the agent of Lyme Disease, because Babesial symptoms tend to be ascribed to Lyme Disease.”
“Physicians caring for patients with moderate to severe Lyme disease should consider obtaining diagnostic tests for Babesiosis and possibly other tick-borne pathogens... especially in patients experiencing "atypical Lyme disease" or patients in whom the response to antibiotic treatment is delayed or absent.”

Krause, PJ, Telford, SR, Spielman, A, et.al. *Concurrent Lyme disease and Babesiosis*. JAMA 1996. 275 (21):1657

“Subjects with evidence of both infections reported a greater array of symptoms than those infected by the spirochete or piroplasm alone.”
“Co-infection generally results in more intense acute illness and a more prolonged convalescence than accompany either infection alone.”
“Spirochete DNA was evident more often and remained in the circulation longer in co-infected subjects than in those experiencing either infection alone.”
“Co-infection might also synergize spirochete-induced lesions in human joints, heart and nerves.”
“Babesial infections may impair human host defense mechanisms”
“The possibility of concomitant Babesial infection should be considered when moderate to severe Lyme Disease has been diagnosed.”

SYMPTOMS

In milder forms, symptoms may include a vague sense of imbalance without true vertigo, headache, mild encephalopathy, fatigue, sweats, air hunger and occasionally cough. When present as a co-infection with Lyme, initial symptoms of the illness are often more acute and severe. Suggestions of co-infection include the above symptoms, but the headaches are more severe, and encephalopathy is out of proportion to the other Borrelia symptoms. The fulminant presentations include high fevers, shaking chills and hemolysis, and can be fatal.

DIAGNOSTIC TESTS

Diagnostic tests are insensitive and problematic. There are at least thirteen Babesial forms found in ticks, yet we can currently only test for B. microti and WA-1 with our serologic and nuclear tests. Standard blood smears reportedly are reliable for only the first two weeks of infection, thus are not useful for diagnosing later infections and milder ones including carrier states where the germ load is too low to be detected.

Krause, PJ, Telford, SR, Spielman, A, et.al. *Concurrent Lyme disease and Babesiosis*. JAMA 1996. 275 (21):1660

“As is common in the case of Babesial infections, parasites frequently cannot be seen in blood films.”

Therefore, multiple diagnostic test methods are available and each have their own benefits and limitations and often several tests must be done. Be prepared to treat based on clinical presentation, even with negative tests.

SEROLOGY

Unlike Lyme, Babesia titers can reflect infection status. Thus, persistently positive titers or western blots suggest persistent infection.

PCR

This is more sensitive than smears for *B. microti*, but will not detect other species.

ENHANCED SMEAR

This utilizes buffy coat, prolonged scanning (up to three hours per sample!) and digital photography through custom-made microscopes. Although more sensitive than standard smears, infections can still be missed. The big advantage is that it will display multiple species, not just *B. microti*.

FLUORESCENT IN-SITU HYBRIDIZATION ASSAY (FISH)

This technique is also a form of blood smear. It is said to be 100-fold more sensitive than standard smears for *B. microti*, because instead of utilizing standard, ink-based stains, it uses a fluorescent-linked RNA probe and ultraviolet light. The Babesial organisms are then much easier to spot when the slides are scanned. The disadvantage is that currently only *B. microti* is detected.

TREATMENT

Treating Babesia infections had always been difficult, because the therapy that had been recommended until 1998 consisted of a combination of clindamycin plus quinine. Published reports and clinical experience have shown this regimen to be unacceptable, as nearly half of patients so treated have had to abandon treatment due to serious side effects, many of which were disabling. Furthermore, even in patients who could tolerate these drugs, there was a failure rate approaching 50%.

Krause, PJ, Spielman, A, Telford, SR et.al.. *Persistent parasitemia after acute Babesiosis* N Engl J Med 1998. 339:162

“Of the treated subjects, almost half had symptoms that were consistent with reactions to quinine, including hearing loss, tinnitus, hypotension, and such gastrointestinal symptoms as anorexia, vomiting, and diarrhea.”

“Although treatment with clindamycin and quinine reduces the duration of parasitemia, infection may persist and recrudescence and side effects are common.”

Because of these dismal statistics, the current regimen of choice for Babesiosis is the combination of atovaquone plus azithromycin. This combination was initially studied in animals, and then applied to Humans with good success, because when atovaquone was used alone, resistance developed in 20% of cases, but reportedly did not occur when azithromycin was added. Fewer than 5% of patients have to halt treatment due to side effects, and the success rate is clearly better than that of clindamycin plus quinine.

The duration of treatment with atovaquone plus azithromycin for Babesiosis varies depending on the degree of infection, duration of illness before diagnosis, the health and immune status of the patient, and whether the patient is co-infected with *Borrelia burgdorferi*. Typically, a three-week course is prescribed for acute cases, while chronic, longstanding infections with significant morbidity and co-infection will require several months of therapy. Relapses have occurred, and retreatment is occasionally needed.

Problems during therapy include diarrhea, mild nausea, the expense of atovaquone (over \$600.00 per bottle — enough for three weeks of treatment), and rarely, a temporary yellowish discoloration of the vision. Regular blood counts, liver panels and amylase levels are recommended during any prolonged course of therapy. Patients who are not cured with this regimen can be retreated but with higher doses, as this has proven effective in many of my patients. Artemesia (a non-prescription herb) may be added, but is not

effective when used alone. Metronidazole can also be added to increase efficacy, but there is minimal clinical data on how much more effective this regimen is.

EHRlichiosis

GENERAL INFORMATION

While it is true that this illness can have a fulminant presentation, and may even become fatal if not treated, milder forms do exist, as does chronic low-grade infection, especially when other tick-borne organisms are present. The potential transmission of Ehrlichia during tick bites is the main reason why doxycycline is now the first choice in treating tick bites and early Lyme, before serologies can become positive. When present alone or co-infecting with *B. burgdorferi*, persistent leukopenia is an important clue. Thrombocytopenia and elevated liver enzymes are less common, but likewise should not be ignored. Headaches, myalgias, and ongoing fatigue seem to relate to this illness, but are extremely difficult to separate from symptoms caused by Bb.

DIAGNOSTIC TESTING

Testing is problematic with Ehrlichia, similar to the situation with Babesiosis. More species are known to be present in ticks than can be tested for with clinically available serologies and PCRs. In addition, serologies and PCRs are of unknown sensitivity and specificity. Standard blood smears for direct visualization of organisms in leukocytes are of low yield. Enhanced smears using buffy coats significantly raises sensitivity and will indicate a wider variety of species. Despite this, infection can be missed, so clinical diagnosis remains the primary diagnostic tool. Again, consider this diagnosis in a Lyme Borreliosis (LB) patient not responding well to therapy.

TREATMENT

Standard treatment consists of Doxycycline, 200 mg daily for two to four weeks. Higher doses, parenteral therapy, and longer treatment durations may be needed based on the duration and severity of illness, and whether immune defects or extreme age is present. However, there are reports of treatment failure even when higher doses and long duration treatment with doxycycline is given. In such cases, consideration may be given for adding rifampin, 600 mg daily, to the regimen.

BARTONELLA

Bartonella henselae, the agent of cat scratch disease, has been found in Ixodid ticks and as a co-infection in patients with Lyme Disease. With co-infection, symptoms of Bartonella are almost impossible to distinguish from Lyme, but may include lymphadenopathy, splenomegaly, hepatomegaly, headache, encephalopathy, somnolence, flu-like malaise, weight loss, sore throat, and a papular or angiomatous rash. In acute cases, there can be hemolysis with anemia, high fever, weakened immune response, jaundice, abnormal liver enzymes, and myalgias. Endocarditis and myocarditis have been reported. More severe infections are associated with immune deficiency and possibly occurrence of opportunistic infections. As in Lyme Disease and Babesiosis, Bartonella may be transmitted to the fetus in the infected pregnant patient.

Diagnostic tests include serology, blood and CSF PCR, and biopsy of skin lesions and lymph nodes.

In the co-infected Lyme patient, eradication may be difficult. Many antibiotic agents have been reported to be effective, including cephalosporins, fluoroquinolones, erythromycins, gentamicin, rifampin and streptomycin. In practice, these patients seem to do best with a combination regimen that utilizes agents that can penetrate cells. Typical combinations include an erythromycin, plus a fluoroquinolone or rifampin. Treatment progress is most commonly assessed by PCR post treatment and serial titers.

NUTRITIONAL SUPPLEMENTS IN DISSEMINATED LYME DISEASE

Studies on patients with chronic illnesses such as Lyme and Chronic Fatigue have demonstrated that some of the late symptoms are related to cellular damage and deficiencies in certain essential nutrients. Double blinded, placebo controlled studies, and in one case direct assay of biopsy specimens have proven the value of some of the supplements listed. Some are required, while others are optional — see below. They are listed in order of importance.

The quality of supplements used is often more important than the dose. In fact, “mega doses” are not recommended. Instead, seek out, if possible, pharmaceutical grade products, especially if USP certified. Pharmanex brand products are recommended because they fit these criteria. In the list below, it is indicated whether the product should be gotten from Pharmanex, or whether a different source or generic substitute is OK. To order Pharmanex brand products, call 1-800-487-1000 and give the following US reference # 9256681.

BASIC DAILY REGIMEN

ACIDOPHILUS (required when on antibiotics)

Essential daily supplement to maintain the normal balance of bowel flora, especially if on antibiotics, or if gastrointestinal disturbances are present. Always try to get enteric coated, milk-free acidophilus. The best kinds are frozen or refrigerated to ensure potency. Take two with each meal.

MULTI-VITAMIN (required)

I recommend the Life Pack family of multivitamins. These are unique supplements — Pharmaceutical grade and USP certified, they are the only products clinically proven in double-blinded, placebo controlled crossover studies to quench free radicals and raise antioxidant levels in the blood and lipids. Choose LifePak for males under 40, LifePak Women for hormonally active women, and LifePak Prime for postmenopausal women and for men over 40. They are available through Pharmanex. Continue long term.

CO-Q10 (ubiquinone) — **required if not taking the prescription drug atovaquone (Mepron)**

Deficiencies have been related to poor function of the heart, limitations of stamina, gum disease, and poor resistance to infections. Heart biopsy studies in Lyme patients indicated that they should take between 200 and 300mg daily of standard CoQ 10, or 90 mg of the well absorbed, highly purified, crystalline CoQ 10 product sold by Pharmanex, (surprisingly, the Pharmanex brand is far less expensive than the generic). The body will manufacture its own COQ 10 when the original illness is controlled, but only if stimulated by aggressive exercise. Therefore, use this supplement until the patient is feeling well and exercising regularly.

VITAMIN B (required)

Clinical studies demonstrated the need for supplement vitamin B in infections with Borrelia, to help clear neurological symptoms. Take one 50 mg B-complex capsule daily. If neuropathy is severe, an additional 50 to 100 mg of B6 daily may be helpful. Generics are OK.

MAGNESIUM (required)

Magnesium supplementation is very helpful for the tremors, twitches, cramps, muscle soreness, heart skips and weakness. It may also help in energy level and cognition. The best source is magnesium L-lactate dehydrate (“Mag-tab SR,” sold by Niche Pharmaceuticals [1-800-677-0355], and available at Wal-Mart). DO NOT rely on “cal-mag,” calcium plus magnesium combination tablets, as they are not well absorbed. Take at least one to two tablet twice daily. Higher doses may cause diarrhea, and you should check with

your physician before using more than this. In some cases, injections or intravenous doses may be necessary. Continue long term.

ESSENTIAL FATTY ACIDS (required)

Studies show that when EFAs are taken regularly, statistically significant improvements in fatigue, aches weakness, vertigo, dizziness, memory, concentration and depression are likely. There are two broad classes: GLA (omega-6 oils) and EPA (omega-3 oils), derived respectively from plant and fish oils. This is what to take:

Plant Oils: borage oil, evening primrose oil, or black currant seed oil (choose one). Do NOT use Flax seed oil!

Fish Oil: Omega-3 (Fish Oil) capsules, 1000 mg per capsule. Use “Optimum Omega” by Pharmanex, if a higher quality product is desired, or to minimize the “fishy” aftertaste.

RECOMMENDATION: four plant oil capsules and four fish oil capsules daily, taken with meals. Continue for three to four months then try to taper down the dose.

OPTIONAL SUPPLEMENTS FOR SPECIAL CIRCUMSTANCES

CORDYMAX (optional)

Cordyceps is a well-known herb from Tibet and has been shown in clinical studies to improve stamina, fatigue, and enhance lung and antioxidant function. It increases mitochondrial ATP levels and also raises superoxide dismutase levels. The positive effects can be so dramatic, I strongly urge all people with fatigue to try this. Available only from Pharmanex as “CordyMax.”

METHYLCOBALAMIN (Methyl B12) (optional)

This is a prescription drug available only from compounding pharmacies. It is related to vitamin B12 and has several documented benefits: it helps to heal damage to the nervous system, enhances diminished T-cell function, can restore the normal diurnal cycle, and can help with memory and cognition. Methyl B12 must be injected into the muscle as it will not be absorbed if swallowed or used sublingually. Dose ranges from 25 to 50 mg daily, based on weight.

REISHI MAX (optional)

This enhanced extract from cracked spores of the reishi mushroom has been shown in clinical studies to augment function of the Natural Killer Cells and macrophages. Take two a day for maintenance, and four a day in disease states. Available only from Pharmanex.

ECHINACEA (optional)

May be helpful in fighting acute and chronic viral illnesses. Choose a pharmaceutical grade brand (“Immune Formula” by Pharmanex), and do not use the liquid form as this contains alcohol. Do not take daily on a long-term basis, as the benefit may wear off. For a chronic illness, double the usual daily dose but take in cycles — use daily three weeks on, one week off each month.

BIO-GINKGO (optional)

The most effective ginkgo brand in my experience — pharmaceutical grade, and very high potency to assure full bioavailability. Available only from Pharmanex. Ginkgo has been shown to increase blood flow to many organs, including the brain. Patients report clearer thinking and better memory. Be aware that this brand is strong — start with a low dose, then increase every few days or a pressure-type, vascular headache may result from all the increased circulation.

GLUCOSAMINE (optional)

Can be of long term benefit to the joints. Do not be misled into buying a product that also contains chondroitin, as this chemical does not add anything, but it can make the product more expensive. Look for a product that contains the herb *Boswellia serrata* — this is a non-irritative anti-inflammatory. Although many generics exist, the Pharmanex product, “Cartilage Formula,” has the right ingredients and is of proven efficacy. Expect improvement only over time (several weeks), but plan to use this indefinitely to maintain joint health.

CREATINE (optional)

Creatine has been shown to be of benefit in neuromuscular degenerative diseases such as Lou Gherig's Disease (ALS) and can be very helpful in supporting low blood pressure, as in NMH. Important: To use this safely, you must have an adequate fluid intake. The creatine product should contain taurine, an amino acid needed to enhance creatine absorption, plus some carbohydrate to aid creatine entry into muscle. You will need a 20 gram loading dose for the first five days, then 4 to 10 grams daily maintenance. Try “Cell Tech” from the Vitamin Shop, and follow label directions.

MILK THISTLE (optional)

Useful to support liver function. Take 175 mg three times daily — use an 80% Silymarin extract.

MUSCLE FIX (optional)

This blend of nutrients from Pharmanex really helps sore, tight muscles. Must be taken on an empty stomach — either two, twice daily between meals, or four at bedtime. Can be used intermittently as needed, or daily.

LYME DISEASE REHABILITATION

Those with long-standing tick borne illnesses end up in poor physical condition. **Even with successful treatment of the infections, chronic Lyme patients will not return to normal unless they pursue a formal program of therapeutic exercise, as outlined below.**

In late stage disease, many negative effects to the body are occurring: muscles atrophy, and to some degree, the heart muscle also suffers, as do the joints, tendons, nerves, etc. The percent fat content of the body as a whole rises, the cholesterol rises, and the balance between HDL and LDL becomes less favorable. In at least 80% of the patients, significant weight gain occurs.

Because of the extreme fatigue and body pain, many Lyme sufferers end up spending inordinate amounts of time in bed, and get far less exercise than they did before they became ill. This begins a debilitating downward spiral that can be very difficult to reverse.

As a result, Lyme patients are stiff, weak, tired, have poor stamina, and are at increased risk for cardiovascular disease and diabetes. Antibiotic treatment alone cannot correct these effects. Therefore, it is necessary to prescribe physical therapy, the extent of which depends on an individual patients' condition, followed by a graded exercise program.

The earliest phase involves multiple modalities (massage, heat, TENS, MENS, ultrasound, etc.) and aggressive range of motion exercises supervised by a physical therapist, to relieve discomfort and to promote better sleep and flexibility. The goal of physical therapy is to prepare the patient for the required, gym-based exercise program. This starts with stretching and mild muscular toning. Then, the program must expand to include muscular conditioning and strengthening, ideally under the supervision of a credentialed exercise physiologist. "Body sculpture" classes are ideal. Aerobics are **not** recommended until the patient has fully recovered.

This is the time for the very best of health habits. I recommend light, low fat food, high in fiber, with high quality nutritional value, minimal amounts of starch and other simple carbohydrates, absolute abstinence from alcohol, elimination of caffeine, and if applicable, a serious commitment to weight loss. Consider testing for food hypersensitivities and recommending books that outline "arthritis diets," as they can help some patients.

Cessation of smoking is extremely important and must be addressed immediately.

As written orders for physical therapy are required to initiate the program, an example of the format of a typical prescription for Lyme rehabilitation follows.

LYME REHAB — PHYSICAL THERAPY PRESCRIPTION

NAME _____

D.O.B. _____ DATE _____

Please enroll this patient in a program of therapy to rehabilitate him/her from the effects of Lyme Disease. If necessary, begin with classic physical therapy, then progress when appropriate to a **whole body** conditioning program. Such therapy must be **graded, carefully individualized, and be performed on a one-on-one basis**, at least initially, to ensure the maximal amount of supervision and guidance.

THERAPEUTIC GOALS (to be achieved in order as the patient's ability allows):

PHYSICAL THERAPY (if needed):

1. Relieve pain and muscle spasms utilizing multiple modalities as available and as indicated: massage, heat, ultrasound, TENS, "micro amp", etc.
2. Increase mobility while protecting damaged and weakened joints, tendons, and ligaments, to increase range of motion and relieve stiffness.
3. **Physical therapy alone is not enough. The role of physical therapy here is to prepare the patient for the required, preferably gym-based, exercise program outlined below.**

EXERCISE Begin with a private trainer for careful direction and education.

PATIENT EDUCATION AND MANAGEMENT (to be done during the initial one-on-one sessions and reinforced at all visits thereafter):

1. Instruct patients on **correct exercise technique**, including proper warm-up, breathing, joint protection, proper body positioning during the exercise, and how to cool-down and stretch afterwards.
2. Please work one muscle group at a time and perform extensive and extended **stretching** to each muscle group immediately after each one is exercised, before moving on to the next muscle group.

3. A careful interview should be performed at the start of each session to make apparent the effects, both good and bad, from the prior visit's therapy, and adjust therapy accordingly.

PROGRAM

1. **Aerobic exercises are NOT allowed**, not even low impact variety, until stamina improves.
2. **Conditioning:** work to improve strength and reverse the poor conditioning that results from Lyme, through a **whole-body** exercise program, consisting of light calisthenics and weight lifting, using small weights and many repetitions. This can be accomplished in exercise classes called "stretch and tone," or "body sculpture," or can be achieved with exercise machines, or carefully with free weights.
3. **Each session should last one hour.** If the patient is unable to continue for the whole hour, then modify the program to decrease the intensity to allow him/her to do so.
4. **Exercise no more often than every other day.** The patient may need to start by exercise every 4th or 5th day initially, and as his/her abilities improve, work out more often, but NEVER two days in a row. The days in between exercise sessions should be spent resting.
5. This **whole-body conditioning program** is what is required to achieve wellness. Simply placing the patient on a treadmill or an exercise bike is not acceptable (except briefly, as part of a warm-up), nor is a simple walking program.

PHYSICIAN'S SIGNATURE _____

MANAGING YEAST OVERGROWTH

Many patients with chronic illnesses including Lyme Disease develop an overgrowth of yeast. A basic strategy to combat this is to eat a full container of sugar-free, non-fruit flavored yogurt that contains active cultures daily, and take acidophilus, two after each meal. Here are some other suggestions:

MOUTH: Yeast problems usually begin in the mouth, for when thrush is present, organisms may repeatedly pass down into the GI tract where they cause the most problems. A tongue with a beige coating, bad breath, and a bad taste in the mouth are signs of oral yeast. Patients should use a toothpaste that contains surfactants (detergent-like cleaning agents), and antiseptic mouthwashes (Scope, Listerine, etc.), and brush the teeth, tongue, gums, cheeks and the roof of the mouth while holding the mouthwash in the mouth.

The most effective treatment, employed as a last resort, consists of using "Dakin's Solution" as a mouth rinse. This is a mixture of household liquid bleach (Clorox), one teaspoon in four ounces of water. A small amount is held in the mouth while brushing, then spit out, and repeated until the thrush has cleared. This is usually a one-time treatment, but may have to be repeated every few weeks.

After using an antiseptic to clean the mouth, it is necessary to immediately eat yogurt or chew an acidophilus capsule to replenish the beneficial flora in the mouth. Because the germ count after such a cleaning will be artificially reduced, and because yeasts are opportunists, they would be the first to come back. By having the yogurt or acidophilus then, a more normal oral flora will result and thrush will be better controlled.

Since yeast germs feed on sugars and starches, avoid simple carbohydrates including sugars, starches, and some fruits. Refer to the diet outlined below.

Prescription medications may be necessary. Mycelex troches and Nystatin liquid are not the best choice, for they contain large amounts of simple sugars. Instead, Nystatin oral powder is preferred, as it does not

contain sugar. It is mixed with water, and swished and swallowed four times daily. Systemic antifungals tablets (Diflucan, Lamisil, Nizoral) may be necessary.

INTESTINAL TRACT: An overgrowth of yeast here will ferment dietary sugars and starches, forming acids, gas, and alcohols. Symptoms include gas, heartburn and/or pain in the stomach area, and because of the alcohol, there can be headaches, dizziness, lightheadedness, wooziness and post-meal fatigue. To clear intestinal yeast, first the oral cavity must be cleared so yeast does not reenter the system with every swallow. Avoid sweets, starches, fruits and juices to starve the germs. Use PLAIN yogurt daily, and acidophilus, 2 capsules three times daily after meals. Systemic antifungal medications may be needed.

VAGINAL: An occasional vaginal yeast infection can be controlled with products such as Monistat cream or suppositories. If it is a recurrent or ongoing problem, then it often reflects a simultaneous intestinal infection, re-infecting the genital area with every bowel movement. Therefore follow the above protocol for intestinal overgrowth, and use topical preparations such as Monistat concurrently for up to two weeks.

YEAST CONTROL DIET (Restricted carbohydrate regimen)

FOODS ALLOWED

Meat, fish, fowl, cheese, eggs, dairy, tofu

FRUITS

- **Only high fiber fruits are allowed**
- **Fruits are only allowed at the end of a meal, and never on an empty stomach**

ALLOWED

Grapefruit, tomatoes, avocado, lemons, limes

SMALL AMOUNTS ONLY! (The high fiber content in these makes up for the carbohydrates)

Pears, apples, strawberries, etc.

NOT ALLOWED

Oranges, watermelons, bananas, grapes, etc. (too much sugar and not enough fiber)

VEGETABLES

Green vegetables and salads are O.K. Avoid starchy vegetables (potato, rice, beans, etc.)

STARCHES

If it is made from flour, it is not allowed! (No breads, cereals, cake, etc.)

SWEETENERS

NOT ALLOWED

No sugars at all; no fructose or corn syrup, and no honey

ALLOWED (if tolerated)

Aspartame, Nutrasweet, Equal; saccharin products allowed but not recommended

DRINKS

ALLOWED

Vegetable juices, water, seltzer, diet sodas, coffee and tea without sugar or caffeine NOT ALLOWED Fruit juices, regular sodas, any drinks sweetened with sugars, syrups or honey