

ADVANCED TOPICS IN LYME DISEASE

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

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DISCLAIMER: The information contained in this monograph is meant for informational purposes only. The management of tick-borne illnesses in any given patient must be approached on an individual basis using the practitioner's best judgment.

TABLE OF CONTENTS

BACKGROUND INFORMATION	
What is Lyme Disease	3
General Principles.....	3
Hypothalamic-Pituitary Axis	4
Co-Infection.....	4
Collateral Conditions.....	5
LYME BORRELIOSIS	
Diagnostic Hints	6
Erythema Migrans.....	7
Diagnosing Later Disease.....	7
The CD-57 Test	8
SYMPTOM CHECKLIST.....	9-10
DIAGNOSTIC CHECKLIST	11
LYME DISEASE TREATMENT GUIDELINES	
LYME BORRELIOSIS	
General Information	12
Treatment Resistance.....	12
Combination Therapy.....	12
Borrelia Neurotoxin	13
TREATING LYME BORRELIOSIS	
Treatment Information.....	13
Antibiotics.....	13
Course During Therapy.....	16
ANTIBIOTIC CHOICES AND DOSES	
Oral Therapy	17
Parenteral Therapy	18
TREATMENT CATEGORIES	
Prophylaxis	19
Early Localized.....	19
Disseminated	19
Chronic Lyme Disease (persistent/recurrent infection)	20
Indicators for Parenteral Therapy	20
ADVANCED TREATMENT OPTIONS	
Pulse Therapy.....	20
Combination Therapy.....	21
LYME DISEASE AND PREGNANCY	21
MONITORING THERAPY AND SAFETY	21
CO-INFECTIONS IN LYME	
Piroplasmiasis (Babesiosis).....	22
Bartonella-Like Organisms.....	23
Ehrlichia/Anaplasma	24
SUPPORTIVE THERAPY	
Rules... ..	25
Nutritional Supplements.....	25
Rehabilitation	27
Rehab/Physical Therapy Prescription.....	29
Managing Yeast Overgrowth	30
BITE PREVENTION AND TICK REMOVAL	32
SUGGESTED READING AND RESOURCES	33

WELCOME!

Welcome to the fifteenth edition of the “Guidelines”.

Amazingly, this edition is not only the fifteenth in the series, but as the first edition appeared in 1984, this reflects *twenty one years of effort!*

Since the last edition, enough new information has become available to justify this revision. New insights regarding co-infections, tests and treatment regimens are included. Nearly every item has been revised, but despite great effort to condense the information, the huge amount of new information included here has resulted in more pages than ever. Information included here is based on the literature, presentations at scientific meetings, the many valuable observations noted by my colleagues, plus experience from caring for my own patients. I have tried to make this information as up-to-date as possible and as inclusive as is practical. Please use the information presented in this document as an information resource and guide. It can never replace your own experience and clinical judgment.

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

BACKGROUND INFORMATION

WHAT IS LYME DISEASE?

I take a broad view of what Lyme Disease actually is. Traditionally, Lyme is defined an infectious illness caused by the spirochete, *Borrelia burgdorferi* (Bb). While this is certainly technically correct, clinically the illness often is much more than that, especially in the disseminated and chronic forms.

Instead, I think of Lyme as the illness that results from the bite of an infected tick. This includes infection not only with *B. burgdorferi*, but the many co-infections that may also result. Furthermore, in the chronic form of Lyme, other factors can take on an ever more significant role- immune dysfunction, opportunistic infections, co-infections, biological toxins, metabolic and hormonal imbalances, deconditioning, etc. I will refer to infection with *B. burgdorferi* as “Lyme Borreliosis” (LB), and use the designation “Lyme” and “Lyme Disease” to refer to the more broad definition I described above.

GENERAL PRINCIPLES

In general, you can think of LB as having three categories: acute, early disseminated, and chronic. The sooner treatment is begun after the start of the infection, the higher the success rate. However, since it is easiest to cure early disease, this category of LB must be taken VERY seriously. Undertreated infections will inevitably resurface, usually as chronic Lyme, with its tremendous problems of morbidity and difficulty with diagnosis and treatment and high cost in every sense of the word. So, while the bulk of this document focuses of the more problematic chronic patient, strong emphasis is also placed on earlier stages of this illness where closest attention and care must be made.

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 LB, these three criteria must be present:

1. Illness present for at least one year (this is approximately when immune breakdown attains clinically significant levels).
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* (Bb), regardless of prior antibiotic therapy (if any).

Chronic Lyme is an altogether different illness than earlier stages, mainly because of the inhibitory effect on the immune system (Bb has been demonstrated *in vitro* to both inhibit and kill B- and T-cells, and will decrease the count of the CD-57 subset of the natural killer cells). As a result, not only is the infection with Bb perpetuated and allowed to advance, but the entire issue of co-infections arises. Ticks may contain and transmit to the host a multitude of potential pathogens. The clinical presentation of Lyme therefore reflects

which pathogens are present and in what proportion. Apparently, in early infections, before extensive damage to the immune system has occurred, if the germ load of the co-infectors is low, and the Lyme is treated, many of the other tick-transmitted microbes can be contained and eliminated by the immune system. However, in the chronic patient, because of the inhibited defenses, the individual components of the co-infection are now active enough so that they too add to features of the illness and must be treated. In addition, many latent infections which may have pre-dated the tick bite, for example herpes viruses, can reactivate, thus adding to the illness.

An unfortunate corollary is that serologic tests can become *less* sensitive as the infections progress, obviously because of the decreased immune response upon which these tests are based. In addition, immune complexes form, trapping Bb antibodies. These complexed antibodies are not detected by serologic testing. Not surprisingly the seronegative patient will convert to seropositive 36% of the time after antibiotic treatment has begun and a recovery is underway. Similarly, the antibody titer may rise, and the number of bands on the western blot may increase as treatment progresses and the patient recovers. Only years after a successfully treated infection will the serologic response begin to diminish.

The severity of the clinical illness is directly proportional to the spirochete load, the duration of infection, and the presence of co-infections. These factors also are proportional to the intensity and duration of treatment needed for recovery. More severe illness also results from other causes of weakened defenses, such as from severe stress, immunosuppressant medications, and severe intercurrent illnesses. **This is why steroids and other immunosuppressive medications are absolutely contraindicated in Lyme. This also includes intra-articular steroids.**

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. Therefore to fully recover not only do all of the active infections have to be treated, but all of these other 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 of these issues and engineering treatments and solutions for all of them will we be able to restore full health to our patients.** Likewise, a patient will not recover unless they are completely compliant with every single aspect of the treatment plan. This must be emphasized to the patient, often on repeated occasions.

It is clear that in the great majority of patients, chronic Lyme is a disease affecting predominantly the nervous system. Thus, careful evaluation may include 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.

HYPOTHALAMIC-PITUITARY AXIS

As an extension of the effect of chronic Lyme Disease on the central nervous system, there often is 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. Interestingly, in a significant number of these patients, successful treatment of the infections can result in a reversal of the hormonal dysfunction, and hormone replacement therapies can be tapered off!

CO-INFECTION

A huge body of research and clinical experience has demonstrated the nearly universal phenomenon in chronic Lyme patients of co-infection with multiple tick-borne pathogens. These patients have been shown to potentially carry Babesia species, Bartonella-like organisms, Ehrlichia, Anaplasma, Mycoplasma, and viruses. Rarely, yeast forms have been detected in peripheral blood. At one point even nematodes were said to be a tick-borne pathogen. 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. In addition, it is known that Babesia infections, like Lyme Borreliosis, are immunosuppressive.

There are changes in the clinical presentation of the co-infected patient as compared to when each infection

is present individually. There may be 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 with many complicating factors. 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.

I must very strongly emphasize that all diagnoses of tick-borne infections remains a clinical one.

Clinical clues will be presented later in this monograph, but testing information is briefly summarized below.

In **Lyme Borreliosis**, western blot is the preferred serologic test. Antigen detection tests (antigen capture and PCR), although insensitive, are very specific and are especially helpful in evaluating the seronegative patient and those still ill or relapsing after therapy. Often, these antigen detection tests are the only positive markers of Bb infection, as seronegativity has been reported to occur in as many as 30% to 50% of cases. Nevertheless, active LB can be present even if all of these tests are non-reactive! Clinical diagnosis is therefore required.

In **Babesiosis**, no single test is reliable enough to be used alone. Only in early infections (less than two weeks duration) can the standard blood smear be helpful. In later stages, one can use serology, PCR, and fluorescent in-situ hybridization ("FISH") assay. Unfortunately, over a dozen other protozoans can be found in ticks, most likely representing species other than *B. microti*, yet commercial tests for only *B. microti* and WA-1 are available at this time! In other words, the patient may have an infection that cannot be tested for. Here, as in *Borrelia*, clinical assessment is the primary diagnostic tool.

In **Ehrlichiosis and Anaplasmosis**, by definition you must test for both the monocytic and granulocytic forms. This may be accomplished by blood smear, PCR and serology. 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, these tests are only an adjunct in making the diagnosis. Rarely, Rocky Mountain Spotted Fever can coexist, and even be chronic. Fortunately, treatment regimens are similar for all agents in this group.

In **Bartonella**, use both serology and PCR. PCR can be performed not only on blood and CSF, but as in LB, can be performed on biopsy specimens. Unfortunately, in my experience, these tests, even when both types are done, will presently miss over half the cases diagnosed clinically.

Frequent exposures to **Mycoplasmas** are common, resulting in a high prevalence of seropositivity, so the best way to confirm active infection is by PCR.

Chronic viral infections may be active in the chronic patient, due to their weakened immune response. PCR testing, and not serologies, should be used for diagnosis. Commonly seen viruses include HHV-6, CMV, and EBV.

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. If neurologic involvement is severe, then consideration should be given to treatment with methylcobalamin (as outlined below in the section on nutritional support).

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 those with severe deficiencies need additional, parenteral dosing: 1 gram IV or IM at least once a week until neuromuscular irritability has cleared.

Pituitary and other endocrine abnormalities are far more common than generally realized. Evaluate fully, including growth hormone levels. Quite often, a full battery of provocative tests is in order to fully define the problem. When testing the thyroid, measure free T3 and free T4 levels and TSH, and 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; clinical hypothyroidism can result from receptor blockade and thus hypothyroidism can exist despite normal serum hormone levels. These may partly account for the dyslipidemia and weight gain that is noted in 80% of chronic Lyme patients. 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. To ensure sustained levels, when T3 is prescribed, have it compounded in a time-release form.

Neurally mediated hypotension (NMH) is not uncommon. Symptoms can include palpitations, lightheadedness and shakiness especially after exertion and prolonged standing, heat intolerance, dizziness, fainting (or near fainting), *and an unavoidable need to sit or lie down*. It is often confused with hypoglycemia, which it mimics. NMH can result from autonomic neuropathy and endocrine dyscrasias. If NMH is present, treatment can dramatically lessen fatigue, palpitations and wooziness, and increase stamina. NMH is diagnosed by tilt table testing. 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. Immediate supportive 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. The long term solution involves restoring proper hormone levels and treating the Lyme to address this and the autonomic dysfunction.

SPECT scanning of the brain- Unlike MRI and CT scans, which show structure, SPECT scans show function. Therefore SPECT scans give us information unattainable through X-rays, CT scans, MRI's, or even spinal taps. In the majority of chronic Lyme Borrelia patients, these scans are abnormal. Although not diagnostic of Lyme specifically, if the scan is abnormal, the scan can not only quantify the abnormalities, but the pattern can help to differentiate medical from psychiatric causes of these changes. Furthermore, repeat scans after a course of treatment can be used to assess treatment efficacy. Note that improvement in scans lag behind clinical improvement by many months.

If done by knowledgeable radiologists using high-resolution equipment, scanning will show characteristic abnormalities in Lyme encephalopathy- global hypoperfusion (may be homogenous or heterogeneous). What these scans demonstrate is neuronal dysfunction and/or varying degrees of cerebrovascular insufficiency. If necessary, to assess the relative contributions of these two processes, the SPECT scan can be done before and after acetazolamide. If the post acetazolamide scan shows significant reversibility of the abnormalities, then vasoconstriction is present, and can be treated with vasodilators, which may clear some cognitive symptoms. Therapy can include acetazolamide, serotonin agonists and even Ginkgo biloba, provided it is of pharmaceutical quality. Therapeutic trials of these may be needed.

Acetazolamide should not be given if there is severe kidney/liver disease, electrolyte abnormalities, pregnancy, sulfa allergy, recent stroke, or if the patient is taking high dose aspirin treatment

LYME BORRELIOSIS

DIAGNOSTIC HINTS

Lyme Borrelia (LB) 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 may be warm. Rarely 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 well-known reference laboratories. 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. In chronic Lyme Borreliosis, the CD-57 count is both useful and important (see below).

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 species-specific ones, but appear later or may not appear at all. You should 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 (on the order of 30%), but specificity is high (greater than 90%).

Spinal taps are not routinely recommended, as a negative tap does not rule out Lyme. Antibodies to Bb are mostly found in Lyme meningitis, and are rarely seen in non-meningitic CNS infection, including advanced encephalopathy. Even in meningitis, antibodies are detected in the CSF in less than 13% 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 (and Bartonella) antigens or nucleic acids are present. It is especially important to look for elevated protein and white 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.

THE CD-57 TEST

Our ability to measure CD-57 counts represents a breakthrough in LB diagnosis and treatment.

Chronic LB infections are known to suppress the immune system and can decrease the quantity of the CD-57 subset of the natural killer cells. As in HIV infection, where abnormally low T-cell counts are routinely used as a marker of how active that infection is, in LB we can use the degree of decrease of the CD-57 count to indicate how active the Lyme infection is and whether, after treatment ends, a relapse is likely to occur. It can even be used as a simple, inexpensive screening test, because at this point we believe that only *Borrelia* will depress the CD-57. Thus, a sick patient with a high CD-57 is probably ill with something other than Lyme, such as a co-infection.

When this test is run by LabCorp (the currently preferred lab, as published studies were based on their assays), we want our Lyme patients to measure above 60; a normal count is above 200. There generally is some degree of fluctuation of this count over time, and the number does not progressively increase as treatment proceeds. Instead, it remains low until the LB infection is controlled, and then it will jump. If the CD-57 count is not in the normal range when a course of antibiotics is ended, then a relapse will almost certainly occur.

CHECK LIST OF CURRENT SYMPTOMS: This is not meant to be used as a diagnostic scheme, but is provided to streamline the office interview. Note the format- complaints referable to specific organ systems and specific co-infections are clustered to clarify diagnoses and to better display multisystem involvement.

Have you had any of the following in relation to this illness? (CIRCLE "NO" OR "YES")

Tick bite N Y "EM" rash (discrete circle) N Y
 Spotted rash over large area N Y Linear, red streaks N Y

SYMPTOM OR SIGN	CURRENT SEVERITY				CURRENT FREQUENCY				
	NONE	MILD	MODERATE	SEVERE	NA	NEVER	OCCASIONAL	OFTEN	CONSTANT
Persistent swollen glands									
Sore throat									
Fevers									
Sore soles, esp. in the AM									
Joint pain									
Fingers, toes									
Ankles, wrists									
Knees, elbows									
Hips, shoulders									
Joint swelling									
Fingers, toes									
Ankles, wrists									
Knees, elbows									
Hips, shoulders									
Unexplained back pain									
Stiffness of the joints or back									
Muscle pain or cramps									
Obvious muscle weakness									
Twitching of the face or other muscles									
Confusion, difficulty thinking									
Difficulty with concentration, reading, problem absorbing new information									
Word search, name block									
Forgetfulness, poor short term memory, poor attention									
Disorientation: getting lost, going to wrong places									
Speech errors- wrong word, misspeaking									
Mood swings, irritability, depression									
Anxiety, panic attacks									
Psychosis (hallucinations, delusions, paranoia, bipolar)									
Tremor									
Seizures									
Headache									
Light sensitivity									
Sound sensitivity									
Vision: double, blurry, floaters									
Ear pain									

SYMPTOM OR SIGN	CURRENT SEVERITY				CURRENT FREQUENCY				
	NONE	MILD	MODERATE	SEVERE	NA	NEVER	OCCASIONAL	OFTEN	CONSTANT
Hearing: buzzing, ringing, decreased hearing									
Increased motion sickness, vertigo, spinning									
Off balance, "tippy" feeling									
Lightheadedness, wooziness, unavoidable need to sit or lie									
Tingling, numbness, burning or stabbing sensations, shooting pains, skin hypersensitivity									
Facial paralysis-Bell's Palsy									
Dental pain									
Neck creaks and cracks, stiffness, neck pain									
Fatigue, tired, poor stamina									
Insomnia, fractionated sleep, early awakening									
Excessive night time sleep									
Napping during the day									
Unexplained weight gain									
Unexplained weight loss									
Unexplained hair loss									
Pain in genital area									
Unexplained menstrual irregularity									
Unexplained milk production; breast pain									
Irritable bladder or bladder dysfunction									
Erectile dysfunction									
Loss of libido									
Queasy stomach or nausea									
Heartburn, stomach pain									
Constipation									
Diarrhea									
Low abdominal pain, cramps									
Heart murmur or valve prolapse?									
Heart palpitations or skips									
"Heart block" on EKG									
Chest wall pain or ribs sore									
Head congestion									
Breathlessness, "air hunger", unexplained chronic cough									
Night sweats									
Exaggerated symptoms or worse hangover from alcohol									
Symptom flares every 4 wks.									
Degree of disability									

DIAGNOSTIC CHECKLIST

To aid the clinician, a workable set of diagnostic criteria were developed with the input of dozens of front line physicians. The resultant document, refined over the years, 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. They should not be misused in an effort to diagnose Lyme or set guidelines for insurance company acceptance of the diagnosis, nor be used to determine eligibility for coverage.**

LYME BORRELIOSIS DIAGNOSTIC CRITERIA	RELATIVE VALUE
Tick exposure in an endemic region	1
Historical facts and evolution of symptoms over time consistent with Lyme.....	2
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 LB 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 the concurrent use 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 and cephalosporinases, 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, imipenem, and vancomycin, which act through different cell wall mechanisms than the penicillins and the cephalosporins.

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.

COMBINATION THERAPY

Treatment of chronic Lyme usually requires combinations of antibiotics. There are four reasons for this:

1. TWO COMPARTMENTS- Bb can be found in both the fluid and the tissue compartments, yet no single antibiotic currently used to treat Bb infections will be effective in both compartments. This is one reason for the need to use combination therapy in the more ill patient. A logical combination might use, for example, azithromycin plus a penicillin.
2. INTRACELLULAR NICHE- Another reason, discussed below, is the fact that Bb can penetrate and remain viable within cells and evade the effects of extracellular agents. Typical combinations include an extracellular antibiotic, plus an intracellular agent such as an erythromycin derivative or metronidazole. Note that some experts discourage the co-administration of bactericidal plus bacteriostatic agents, thus the recommendation to avoid a cell wall drug combined with a tetracycline.
3. L-FORMS (SPHEROPLAST)- It has been recognized that B. burgdorferi can exist in at least two, and possibly three different morphologic forms: spirochete, spheroplast (or I-form), and the recently discovered cystic form (presently, there is controversy whether the cyst is different from the I-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 the advanced erythromycin derivatives. Apparently, Bb can shift among the three forms during the course of the infection. Because of this, it may be necessary to cycle different classes of antibiotics and/or prescribe a combination of dissimilar agents.
4. CYSTIC FORM- When present in a hostile environment, such as growth medium lacking some nutrients, spinal fluid, or serum with certain antibiotics added, Bb can change from the spiral form

("spirochete") into a cyst form. This cyst seems to be able to remain dormant, but when placed into an environment more favorable to its growth, Bb can revert into the spirochete form. The antibiotics commonly used for Lyme do not kill the cystic form of Bb. However, there is laboratory evidence that metronidazole and tinidazole will disrupt it. Therefore, the chronically infected patient who has resistant disease may need to have metronidazole (or tinidazole) added to the regimen. More details are provided in the section on treatment options.

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.

Two prescription medications that can bind these toxins include cholestyramine resin and Welchol pills. When taken 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 can continue for a month or more. Retreatment is always possible.

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 a half hour before, to two hours after a dose of one of these fiber agents.

Cholestyramine should be taken two to 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.

TREATING LYME BORRELIOSIS

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 antibiotic blood level measurements and clinical response.

ANTIBIOTICS

There are four 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. Kill kinetics indicate that a large spike in blood and tissue levels is more effective than sustained levels, which is why with doxycycline, oral doses of 200 mg bid is more effective than 100 mg qid. Likewise, this is why IV doses of 400 mg once a day is more effective than any oral regimen.

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. With cell wall agents such as the penicillins, kill kinetics indicate that sustained bactericidal levels are needed for 72 hours to be effective. Thus the goal is to try to achieve sustained blood and tissue levels. However, since blood levels are extremely variable among patients, they should be measured. Because of its short half-life and need for high levels, amoxicillin is usually administered along with probenecid. An attractive alternative is benzathine penicillin ("Bicillin-LA"). This is an intramuscular depot injection, and although doses are relatively small, the sustained blood and tissue levels are what make this preparation so effective.

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 relatively long half-life. Cephalosporins 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. Because this agent's G.I. side effects and high cost, it is not often used as first line drug. As with the penicillins, try to achieve high, sustained blood and tissue levels by frequent dosing and/or the use of probenecid. Measure blood levels when possible.

When choosing a third generation cephalosporin, there are several points to remember: Ceftriaxone is administered twice daily (an advantage for home therapy), but 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, so the current recommendation is to administer it four days in a row each week. Cefotaxime, which must be given at least every eight hours or as a continuous infusion, is less convenient, but as it has only 5% biliary excretion, it never causes biliary concretions, and may have less impact on gut flora.

ERYTHROMYCIN has been shown to be almost ineffective as monotherapy. The azalide azithromycin is somewhat more effective but still poorly effective when given orally. As an IV drug, much better results are seen. Clarithromycin is more effective as an oral agent than azithromycin, but can be difficult to tolerate due to its tendency to promote yeast overgrowth, bad aftertaste, and poor GI tolerance at the high doses needed. These problems are much less severe with the ketolide telithromycin, which is generally well tolerated.

Erythromycins (and the advanced generation derivatives mentioned above) have impressively low MBCs and they do concentrate in tissues and penetrate cells, so they theoretically should be ideal agents. However, erythromycin is ineffective, initial clinical results with azithromycin (and to a lesser degree, clarithromycin) have been disappointing. 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 azithromycin and clarithromycin. 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.

Telithromycin, on the other hand, is stable in the intracellular acid environment, which may be why this is currently by far the most effective drug of this class, and may replace the others in the majority of patients with LB. Likewise, there is no need to co-administer amantadine or hydroxychloroquine. This antibiotic has other advantages- it has been engineered to prevent drug resistance, has almost no negative impact on E. coli in the intestinal tract (hopefully minimizing the risk for diarrhea), and it can be taken with or without food.

However, there are disadvantages:

1. May interact with a wide variety of medications because it is an inhibitor of the cytochrome CYP3A4. It is vital that this be taken into account as many Lyme patients take a variety of medications concurrently, and often from several practitioners.
2. May lengthen the QT interval. This should be measured prior to prescribing this drug, and if borderline, rechecked after it is begun.
3. Can transiently cause blurry vision, delayed accommodation, and even double vision.
4. Liver enzymes may become elevated. Blood tests should be done regularly to monitor this.
5. The usual precautions of any antibiotic also still apply- risk for allergy, stomach upset, Herxheimer reactions, etc.

QTc INTERVAL

- QTc is the QT corrected for heart rate
- Measure the precordial lead that has the best T wave (usually V-2 or V-5)
- Measure from the start of the Q wave to the end of the T wave
- QT interval is inversely related to the heart rate (slow pulse results in a longer QT)
- $QTc = QT \div \sqrt{RR \text{ interval}}$
- Normals: Females <450 ms, Males < 470 ms
- Want $K^+ > 4.0$, $Mg^{++} > 2.0$; avoid hypocalcemia

METRONIDAZOLE (Flagyl) When present in a hostile environment, such as growth medium lacking some nutrients, spinal fluid, or serum with certain antibiotics added, Bb can change into a cyst form. This cyst seems to be able to remain dormant, but when placed into an environment more favorable to its growth, the cyst can revert into the spirochete form. The conventional antibiotics used for Lyme, such as the penicillins, cephalosporins, etc do not kill the cystic form of Bb, yet there is laboratory evidence that metronidazole will kill it. 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 Flagyl, this class of medication should not be used in these two- and three-drug regimens. Some clinicians favor tinidazole as this may be equally effective but result in fewer side effects. However, this has yet to be documented.

Important precautions:

1. Pregnancy while on Flagyl 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 symptoms.
3. Yeast overgrowth is especially common. A strict anti-yeast regimen must be followed.
4. Flagyl can be irritative to the nervous system- in the short term, it may cause irritability, "spacey" feelings, etc. Longer term, it can affect the peripheral nerves, causing tingles, numbness, etc. If mild, a change in dose may be required. Often, extra vitamin B can clear these symptoms. If the nerve symptoms persist or are strong, then metronidazole must be discontinued or these symptoms may become very long lasting.
5. Strong Herxheimer-like reactions are seen in almost everyone.

RIFAMPIN is a well-known antibiotic that has been in use for many decades. It is primarily used to treat tuberculosis, but also has been used in other conditions, such as prevention of meningitis in those exposed, for treating resistant Staph, etc. Potentially, rifampin may be effective in treating Bartonella, Ehrlichia, Mycoplasma, and Borrelia. There are as yet no formal clinical studies on the use of this medication in these illnesses, but many patients have been treated with rifampin and have had favorable results. When used, regular blood tests (CBC, liver enzymes) are usually performed to monitor for side effects. Rifampin can also discolor urine, tears and sweat (brownish-orange). It may also stain some types of water-permeable contact lenses. Taking rifampin during pregnancy is not advised. Finally, because this drug is an inducer of cytochromes (CYP3A4), co-administration with other medications may result in lower and more brief blood levels of the co-administered drug. Thus, be aware of these potential drug interactions.

BENZATHINE PENICILLIN Comparative studies published by Fallon et. al. at Columbia University have shown that parenteral therapy is superior to oral therapy in chronic patients. Options include intramuscular long acting penicillin G (benzathine penicillin, or "Bicillin-LA") or intravenous antibiotics.

For an antibiotic in the penicillin class to be effective, time-killing curves show that significant levels of antibiotic must be sustained for 72 hours. Bicillin LA is a sustained release formulation that meets these criteria.

Published studies in children and adults, combined with over a decade of experience with this therapy by front line, Lyme-treating physicians have established the efficacy, safety and usefulness of this medication. In many patients it is more effective than oral antibiotics for treating Lyme, and compares closely to intravenous therapy in terms of efficacy if the dose is high enough.

It is usually administered three or four times weekly for six to twelve months. It has the advantage of being relatively inexpensive, free of gastrointestinal side effects, unlikely to promote the overgrowth of yeast, and has an excellent safety record spanning many decades.

Finally, an added plus is that family members can be trained to administer this treatment at home.

CEFTRIAXONE TREATMENT A subset of patients who have severe, longstanding illness due to *Borrelia burgdorferi* carry persistent infection despite having previously received antibiotic treatments which have eliminated the disease in less ill individuals. The mechanism for such persistence has been the subject of many peer reviewed articles. They include persistence of *B. burgdorferi* in protective niches, inhibition and lysis of lymphocytes, survival in phagocytic vacuoles, antigenic shifts, slow growth, shifting into alternate forms, and dormancy and latency.

One successful approach in the more ill patient, published in the early 1990s, is to use higher doses of ceftriaxone in a pulsed-dose regimen. Since then, clinical experience has expanded upon this concept, and at the MLDA Lyme Congress in September, 2002, Cichon presented data on a pulsed, high dose regimen which supports and refines this concept. This regimen is now considered the current standard of care in the use of ceftriaxone.

Treatment with ceftriaxone is dosed at 4 grams daily- given either as 2 grams IV twice daily, or 4 grams slowly once a day, four days in a row each week, usually for 14 or more weeks. Such a regimen is not only more effective in the Chronic Lyme patient, but regular interruptions in treatment lessen the potential complications of intensive antibiotic therapy with ceftriaxone, such as biliary sludging and colitis. Hence a more effective, safer regimen that by virtue of the treatment breaks, is less costly and affords the patient a more acceptable lifestyle. IV access with a heparin lock becomes possible (and preferred).

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 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 for years 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 Jarisch 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 and 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 I.V. 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 I.V. 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 I.V. treatment. In general, I.V. therapy is given until there is a clear positive response, and 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 I.V. 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, and sleep deprivation. Advise them to take a break when (or ideally before) the inevitable mid afternoon fatigue sets in (napping is encouraged).

All patients must keep a carefully detailed daily diary of their symptoms to help us document the presence of the classic four week cycle, judge the effects of treatment, and determine 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.

ANTIBIOTIC CHOICES AND DOSES

ORAL THERAPY: Always check blood levels when using agents marked with an *, and adjust dose to achieve a peak level above ten and a trough greater than three. Because of this, the doses listed below may have to be raised. Consider Doxycycline first in early Lyme due to concern for Ehrlichia co-infections.

*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: 200 mg bid 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 or change to another drug.
- *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.
 - Azithromycin- 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 or in younger children.
Overall, poor results when administered orally
 - Clarithromycin- Adults: 250 to 500 mg q6h plus hydroxychloroquine, 200-400 mg/d, or amantadine 100-200 mg/d. Cannot be used in pregnancy or in younger children.
Clinically more effective than azithromycin
 - Telithromycin- Adolescents and adults: 800 mg once daily
Do not need to use amantadine or hydroxychloroquine
So far, the most effective drug of this class, and possibly the best oral agent if tolerated. Expect strong and quite prolonged Herxheimer reactions.
Must watch for drug interactions (CYP3A-4 inhibitor), check the QTc interval, and monitor liver enzymes.
Not to be used in pregnancy.
 - *Augmentin- Standard Augmentin cannot exceed three tablets daily due to the clavulanate, thus is given with amoxicillin, so that the total dose of the amoxicillin component is as listed above for amoxicillin. This combination can be effective when Bb beta lactamase is felt to be significant.
 - *Augmentin XR 1000- This is a time-release formulation and thus is a better choice than standard Augmentin.
Dose- 1000 mg q 8 h, to 2000 mg q 12 h based on blood levels.
 - Chloramphenicol- Not recommended as not proven and potentially toxic.
 - Metronidazole: 500 to 1500 mg daily in divided doses. Non-pregnant adults only.

PARENTERAL THERAPY

- Ceftriaxone- Risk of biliary sludging (therefore often Actigall is co-administered- one to three tablets daily).
Adults and pregnancy: 2g q12 h, 4 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: 6g to 12g daily. Can be given q 8 h as divided doses, but a continuous infusion may be more efficacious. When exceeding 6 g daily, use pulsed-dose schedule
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 blood levels are higher when given parenterally and single large daily doses optimize kinetics of killing with this drug.
Always measure blood levels.
Adults: Start at 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 to four doses weekly.
Adolescents: 1.2 to 3.6 million U weekly.
May be used in pregnancy.
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.
Primaxin and Unisyn- similar in efficacy to cefotaxime, but often work 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, how it was removed, and length of attachment (anecdotally, as little as four hours of attachment can transmit pathogens). 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 co-infection!):

- 1) Adults: Oral therapy for 28 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 28 days.

EARLY LOCALIZED - Single erythema migrans with no constitutional symptoms:

- 1) Adults: oral therapy- must continue until symptom and sign free for at least one month, with a 6 week minimum.
- 2) Pregnancy: 1st and 2nd trimesters: I.V. X 30 days then oral X 6 weeks
3rd trimester: Oral therapy X 6+ weeks as above.
Any trimester- test for Babesia 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 steroid treatment:

- 1) Adults: oral therapy until no active disease for 4 to 8 weeks (4-6 months typical)
- 2) Pregnancy: As in localized disease, but treat throughout pregnancy.
- 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: I.V. therapy until clearly improved, with a 6 week minimum. Follow with oral therapy or IM benzathine penicillin until no active disease for 6-8 weeks. I.V. 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 I.V. therapy (14 or more weeks), then oral or IM, if effective, to same endpoint. Combination therapy with at least two dissimilar antibiotics almost always needed.
- 2) Children: IV therapy for 6 or more weeks, then oral or IM follow up as above. Combination

therapy usually needed.

CHRONIC LYME DISEASE (PERSISTENT/RECURRENT INFECTION)

By definition, this category consists of patients with active infection, of a more prolonged duration, who are more 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 for all of these, and search for concurrent infections including viruses, chlamydias, and mycoplasmas. Be sure to do an endocrine workup if indicated. 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 and exercise 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 in this select group is thus mandatory.

In patients who have chronic Lyme, who do not fully respond to antibiotics, one must search for an explanation. In many cases, these patients are found to have pituitary insufficiency of varying degrees. The abnormalities may be extremely subtle, and provocative testing must be done for full diagnosis. Persistent fatigue, limited stamina, hypotension, and loss of libido suggest this possibility.

Similarly, a small but significant number of these patients harbor toxic levels of heavy metals. Challenge testing by knowledgeable, experienced clinicians is necessary for evaluation. Treatment must be directed toward correcting the specific abnormalities found, and post-treatment retesting to assess efficacy of treatment and endpoint of therapy should be done. Suspect this when poor immune responsiveness and persistent neuropathic signs and symptoms are present.

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 while infected with Bb.
- Major neurological involvement
- Active synovitis with high sedimentation rate
- Elevated protein or cells in the CSF

ADVANCED TREATMENT OPTIONS

PULSE THERAPY consists of administering antibiotics (usually parenteral ones) two to four days in a row per week. 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. 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. 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.

COMBINATION THERAPY (see page 12)

This consists of using two or more dissimilar antibiotics simultaneously for antibiotic synergism, to better compensate for differing killing profiles and sites of action of the individual medications, and to cover the three known forms of Bb. A typical combination is the use of a cell wall agent plus a protein inhibitor (ie: amoxicillin plus clarithromycin). Note that 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.

LYME DISEASE AND PREGNANCY

It is well known that *B. burgdorferi* can cross the placenta and infect the fetus. In addition, breast milk from infected mothers has been shown to harbor spirochetes that can be detected by PCR and grown in culture.

The Lyme Disease Foundation in Hartford, CT had kept a pregnancy registry for eleven years beginning in the late 1980s. They found that if patients were maintained on adequate doses of antibiotic therapy during gestation, then no babies were born with Lyme. My own experience over the last twenty years agrees with this.

The options for treating the mother include oral, intramuscular, and intravenous therapy as outlined above. It is vital that peak and trough antibiotic levels be measured if possible at the start of gestation and at least once more during treatment.

During pregnancy, symptoms generally are mild as the hormonal changes seem to mask many symptoms. However, post-partum, mothers have a rough time, with a sudden return of all their Lyme symptoms including profound fatigue. Post partum depression can be particularly severe. I always advise help in the home for at least the first month, so adequate rest and time for needed treatments are assured.

I also advise against breast feeding for obvious reasons as mentioned above.

MONITORING THERAPY

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

SAFETY

Over 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. Be sure to test stool for both toxin A and toxin B when evaluating for *C. difficile* colitis.

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

It had been thought that *Babesia microti* is the only significant piroplasm affecting humans. Now it is believed that many of the over two dozen known species of piroplasms can be carried by ticks and potentially be transmitted to the human. Unfortunately, we have no widely available tests for these non-*microti* species. That is why, again, a clinical diagnosis is required.

Piroplasms 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, and especially if they are experiencing atypical symptoms, suspect a co-infection. From the literature:

- "Co-infection generally results in more intense acute illness, a greater array of symptoms, 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."
- "Babesia infections may impair human host defense mechanisms..."
- "The possibility of concomitant Babesia infection should be considered when moderate to severe Lyme Disease has been diagnosed."

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 serologic evidence of co-infection with *Babesia microti*. It has also been reported that *Babesia* infections can range in severity from mild, subclinical infection, to fulminant, potentially life threatening illness. Subclinical infection is often missed because the symptoms are incorrectly ascribed to Lyme. *Babesia* infections, even mild ones, may recur even after treatment and cause severe illness. This phenomenon has been reported to occur at any time, including up to several years after the initial infection! Furthermore, such *Babesia* carriers pose a risk to the blood supply as this infection has been reported to be passed on by blood transfusion.

SYMPTOMS

Clues to the presence of Babesiosis include a more acute initial illness- patients often recall a high fever and chills at the onset of their Lyme. Over time, they can note night sweats, air hunger, an occasional cough, persistent migraine-like headache, a vague sense of imbalance without true vertigo, encephalopathy and fatigue. The fulminant presentations are seen in those who are immunosuppressed, especially if asplenic, and in advanced ages. They include high fevers, shaking chills and hemolysis, and can be fatal.

DIAGNOSTIC TESTS

Diagnostic tests are insensitive and problematic. There are at least thirteen, and possibly as many as two

dozen Babesia 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. 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 Babesia 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%.

Because of these dismal statistics, the current regimen of choice for Babesiosis is the combination of atovaquone (Mepron, Malarone), 750 mg bid, plus an erythromycin-type drug, such as azithromycin (Zithromax), clarithromycin (Biaxin), or telithromycin (Ketek) in standard doses. This combination was initially studied in animals, and then applied to Humans with good success. 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 combinations 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 a minimum of four 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. Blood counts, liver panels and amylase levels are recommended every three weeks during any prolonged course of therapy as liver enzymes may elevate. Treatment failures usually are related to inadequate atovaquone levels. Therefore, patients who are not cured with this regimen can be retreated with higher doses (and atovaquone blood levels can be checked), as this has proven effective in many of my patients. Artemesia (a non-prescription herb) should be added in all cases. Metronidazole or Bactrim can also be added to increase efficacy, but there is minimal clinical data on how much more effective this will be.

BARTONELLA-LIKE ORGANISMS

It has been said that Bartonella is the most common of all tick-borne pathogens. Indeed, there seems to be a fairly distinct clinical syndrome when this type of organism is present in the chronic Lyme patient. However, several aspects of this infection seem to indicate that this tick-associated strain of Bartonella is different from that described as "cat scratch disease". For example, in patients who fit the clinical picture, standard Bartonella blood testing is commonly non-reactive. Furthermore, the usual Bartonella medications do not work for this- they suppress the symptoms but do not permanently clear them. For these reasons I like to refer to this as a "Bartonella-like organism" (BLO), rather than assume it is a more common species.

Indicators of BLO infection include CNS symptoms out of proportion to the other systemic symptoms of chronic Lyme. There seems to be an increased irritability to the CNS, with agitation, anxiety, insomnia, and even seizures, in addition to other unusually strong symptoms of encephalitis, such as cognitive deficits and confusion. Other key symptoms may include gastritis, lower abdominal pain (mesenteric adenitis), sore soles, especially in the AM, tender subcutaneous nodules along the extremities, and red rashes. These rashes may have the appearance of red streaks like stretch marks that do not follow skin planes, spider veins, or red papular eruptions. Lymph nodes may be enlarged and the throat can be sore.

Because standard Bartonella testing, either by serology or PCR, may not pick up this BLO, the blood test is very insensitive. Therefore, the diagnosis is a clinical one, based on the above points. Also, suspect infection with BLO in extensively treated Lyme patients who still are encephalitic, and who never had been treated with a significant course of specific treatment.

The drug of choice to treat BLO is levofloxacin. Levofloxacin is usually never used for Lyme or Babesia, so many patients who have tick-borne diseases, and who have been treated for them but remain ill, may in fact be infected with BLO. Treatment consist of 500 mg daily (may be adjusted based on body weight) for at least one month. Treat for three months or longer in the more ill patient. It has been suggested that levofloxacin may be more effective in treating this infection if a proton pump inhibitor is added in standard doses.

Another subtlety is that certain antibiotic combinations seem to inhibit the action of levofloxacin, while others seem to be neutral. I advise against using an erythromycin-like drug, as clinically such patients do poorly. On the other hand, combinations with cephalosporins, penicillins and tetracyclines are okay. Alternatives to levofloxacin include rifampin, gentamicin and possibly streptomycin.

Levofloxacin is generally well tolerated, with almost no stomach upset. Very rarely, it can cause confusion- this may be relieved by lowering the dose. There is, however, one side effect that would require it to be stopped- it may cause a painful tendonitis, usually of the largest tendons. If this happens, then the levofloxacin must be stopped or tendon rupture may occur. Unfortunately, levofloxacin and drugs in this family cannot be given to those under the age of 18, so other alternatives, such as azithromycin, are used in children.

Incidentally, animal studies show that Bartonella may be transmitted across the placenta. No human studies have been done.

EHRlichia (AND ANAPLASMA)

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, common in acute infection, are less often seen in those who are chronically infected, but likewise should not be ignored. Headaches, myalgias, and ongoing fatigue suggest 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 raise sensitivity and can detect 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 Lyme therapy who has symptoms suggestive of Ehrlichia.

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.

SUPPORTIVE THERAPY

CERTAIN **ABSOLUTE RULES** MUST BE FOLLOWED IF LYME SYMPTOMS ARE TO BE PERMANENTLY CLEARED:

1. Not allowed to get behind in sleep, or become overtired.
2. No caffeine or other stimulants that may affect depth or duration of sleep, or reduce or eliminate naps.
3. Absolutely no alcohol!
4. No smoking at all.
5. Aggressive exercises are required and should be initiated as soon as possible.
6. Diet must contain generous quantities of high quality protein and be high in fiber and low in fat and carbohydrates- no simple carbohydrates are allowed. Instead, use those with low glycemic index.
7. Certain key nutritional supplements should be added.
8. COMPLIANCE!

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.

I have found that the quality of supplements used is often more important than the dose. In fact, I do not recommend "mega doses". Instead, seek out, if possible, pharmaceutical grade products, especially if USP certified. I recommend Pharmanex products because they fit these criteria. In the list below, it is indicated whether the products should be gotten from Pharmanex, or whether a different source, or even a generic substitute is OK. To order Pharmanex products, call 1-800-487-1000 and give the following U.S. reference number: 9256681-R.

BASIC DAILY REGIMEN (in order of importance)

PROBIOTICS (required when on antibiotics)

Essential to maintain the normal balance of intestinal flora; Acidophilus: the best kinds are frozen or refrigerated to ensure potency. Take two with each meal. Plan to mix together several different brands to broaden the spectrum. You can get acidophilus from most vitamin stores. An alternative that does not need refrigeration and can be taken only once a day is a high potency, patented product called "Pro Bio" from Pharmanex. In addition drink "Kefir", 2 to 4 ounces a day on occasion, and have 4 ounces of sugar-free yogurt daily if possible.

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, LifePak Prenatal when pregnant, and LifePak Prime for postmenopausal women and for men over 40. LifePak Teen is also available. They are available through Pharmanex. Continue long term.

CO-Q10- required, but do not use while taking the prescription drug atovaquone (Mepron, Malarone).

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 120 mg (four caplets) of the well absorbed, highly purified, crystalline CoQ 10 product sold by Pharmanex, (surprisingly, the Pharmanex brand is less expensive than the generic!).

ALPHA LIPOIC ACID (required)

This facilitates entry of CoQ-10 into mitochondria. Dose is 300 mg twice daily. Generic is OK.

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 mg of B-6 can be added. 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 tablet twice daily. Higher doses increase the benefit and should be tried, but may cause diarrhea. In some cases, intramuscular or intravenous doses may be necessary.

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 Oil: Use a refrigerated product of mixed omega oils obtained from the local health food store. Take one to two tablespoons daily. May be mixed with food, put on salads, etc.

Fish Oil: Use "Marine Omega" by Pharmanex. Use four daily, taken on a full stomach (this brand is required).

OPTIONAL SUPPLEMENTS FOR SPECIAL CIRCUMSTANCES

FOR NEUROLOGIC SYMPTOMS

ACETYL-L-CARNITINE- this is taken along with SAM-e. This combination can result in noticeable gains in short term memory, mood and cognition. The Acetyl Carnitine also is said to help heart and muscle function. Doses: Acetyl-L-carnitine- 1500-2000 mg daily on empty stomach. SAM-e- 400 mg daily with the acetyl carnitine. Available in most vitamin stores. Positive results may appear as early as 3 weeks; use for 2 to 3 months. May be repeated if needed; generics are okay.

METHYLCOBALAMIN (Methyl B12)

Methylcobalamin is a prescription drug derived from vitamin B12. This can help to heal problems with the central and peripheral nervous system, improve depressed immune function, and help to restore more normal sleeping patterns. Many patients note improved energy as well. Because the oral form is not absorbed when swallowed or dissolved under the tongue, Methyl B12 must be taken by injection. Dose is generally 25 mg. (1 c.c.) daily for 3 to 6 months. Long term studies have never demonstrated any side effects from this drug. However, the urine is expected to turn red shortly after each dose- if the urine is not red, a higher dose may be needed or the present supply may have lost potency. The injectable form of this is not available in regular drug stores. It must be manufactured (compounded) by specialty pharmacies on order.

FOR INCREASED ANTIOXIDANT LEVELS

GREEN TEA

Green, but not black tea contains some of the most potent antioxidants around (80-100 times more effective than vitamin C). At least four cups daily are needed to reap this benefit. I strongly suggest you get only caffeine-free tea. A nice alternative is "TeGreen" capsules by Pharmanex. They contain 97% pure tea polyphenols and each capsule is the equivalent of four to seven cups of decaffeinated green tea. Take one or two daily.

CORDYMAX

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 also raises superoxide dismutase levels, important to

prevent lesions in the central nervous system. The positive effects can be dramatic; can be used long term. Available from Pharmanex as "CordyMax".

FOR IMMUNE SUPPORT

"REISHI MAX "

This enhanced extract from cracked spores of the reishi mushroom has been shown in clinical studies to augment function of the Natural Killer Cells as well as macrophages. Recommended in all patients who have a CD-57 count below 60. Take four a day. Available only from Pharmanex.

FOR FATIGUE

Alpha Lipoic Acid, CordyMax, Co Q-10, Methylcobalamin

FOR JOINT SYMPTOMS

GLUCOSAMINE

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.

VITAMIN C

If high doses are to be used, split them into several separate doses, and consider using "Ester-C" (non-acid and longer acting), or "C-Salts" (very well tolerated)

FLEX CREAM

An amazing liniment-like product that really works and has a money back guarantee. Use for any type of body pain- spread on a thick layer and do not rub in. Takes 30 to 60 minutes to work, then lasts many hours. A Pharmanex exclusive.

OTHER OPTIONAL SUPPLEMENTS

CREATINE

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. It may also benefit strength, stamina, and heart function. 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 daily- use an 80% Silymarin extract. Available from many vitamin stores.

LYME DISEASE REHABILITATION

Despite antibiotic treatments, patients will NOT return to normal unless they exercise! This is because in most cases the chronic Lyme patient is deconditioned. More importantly, a properly executed exercise program becomes part of the treatment, as it can actually go beyond the antibiotics in helping to clear the symptoms and to maintain a remission.

Therefore, a vital part of any plan for recovery must include serious efforts at physical reconditioning. This may begin with physical therapy: the physical therapy should involve massage, heat, ultrasound and simple range of motion exercises to relieve discomfort and promote better sleep and flexibility. Ice and electrical stimulation should not be used!

The program ultimately must evolve into a graded, strenuous exercise program that consists of a specific regimen of *non-aerobic* conditioning- see below.

Although the scientific basis for the benefits of exercises is not known, there are several reasonable theories.

It is known that Bb will die if exposed to all but the tiniest oxygen concentrations. If an aggressive exercise program can increase tissue perfusion and oxygen levels, then this may play a role in what is being seen. Also, during aggressive exercise, the core body temperature can rise above 102 degrees; it is known that *B. burgdorferi* is very heat sensitive. Perhaps it is the added tissue oxygenation, or higher body temperature, or

the combination that weakens the Lyme Borrelia, and allows the antibiotics and our defenses to be more effective. In addition, there is now evidence that a carefully structured exercise program may benefit T-cell function in the immune system, an obvious potential benefit in an illness like Lyme that is known to weaken immune responses. To reap this benefit, the exercise sessions should last at least one hour, but never be repeated more often than every other day. The following pages is an exercise prescription that outlines these recommendations in detail. NOTE: a cardiac stress test may be necessary prior to exercising to ensure safety.

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 chronic tick-borne diseases. If necessary, begin with classic physical therapy, then progress when appropriate to a **whole body conditioning program**.

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

PHYSICAL THERAPY (if needed):

1. **The role of physical therapy here is to prepare the patient for the required, preferably gym-based exercise program outlined below.**
2. Relieve pain and muscle spasms utilizing multiple modalities as available and as indicated: massage, heat, ultrasound, and passive and active range of motion. DO NOT use ice or electrical stim unless specifically ordered by our office. Paraffin baths can be quite useful.
3. Increase mobility, tone and strength while protecting damaged and weakened joints, tendons, and ligaments, and teach these techniques to the patient. Use light weights/minimal resistance but a lot of repetitions in any exercises prescribed. Aerobics are not permitted. Transition the patient slowly to the gym-based program outlined below.
4. Please see the patient two days per week- but do not schedule two days in a row!

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 exercising every 4th or 5th day initially, and as abilities improve, work out more often, but NEVER two days in a row. The non-exercise days 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 weakened defenses, such as from chronic illnesses, including Lyme Disease, develop an overgrowth of yeast. This begins in the mouth and then spreads to the intestinal tract. Therefore the primary line of defense is careful oral hygiene, replenishing the beneficial bacteria by daily intake of yogurt, Kefir, and/or acidophilus, and by following a strict low carbohydrate diet.

ORAL HYGEINE:

CLEANSING

Brush the teeth, tongue, gums, inner cheeks and palate first with toothpaste, then again for 30 seconds while holding an antiseptic mouthwash in the mouth. Then, rinse by scrubbing while holding plain water in the mouth.

TOOTHPASTE

Use "AP-24" toothpaste, sold by NuSkin Enterprises. Unlike conventional toothpastes that may contain alcohols, formaldehydes and abrasives, this product cleans in a unique way. It contains two "surfactants" (detergent-like cleansers) that are very effective without being harsh. This product is available in two forms- regular and whitening (both contain fluoride). Choose either one.

In addition, get from them their patented toothbrush that is designed to work with this toothpaste. It cleans better and is far gentler than regular or electric toothbrushes.

Order AP-24 products by calling 1-800-487-1000. The U.S. reference # is 9256681-R

MOUTHWASHES

Use an antiseptic mouthwash (Scope, Listerine, etc.), and brush the teeth, tongue, gums, cheeks and the roof of the mouth while holding the mouthwash in the mouth. Do this for 30 seconds, then rinse repeatedly with water.

For especially thick or resistant thrush, the most effective (and drastic) treatment, employed as a last resort, consists of using "Dakin's Solution" as a mouth rinse. Make this by mixing one teaspoon of household liquid bleach (Clorox) 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, it is necessary to immediately eat yogurt or chew an acidophilus capsule to replenish the beneficial flora in the mouth. Because the germ count, both harmful and beneficial, will be artificially reduced after such a cleaning, and because yeasts are opportunists, the yeast infection can come back. By having the yogurt or acidophilus then, the yeast will be crowded out and a more normal oral flora will result.

INTESTINAL TRACT: An overgrowth of yeast here will ferment dietary sugars and starches, forming acids, gas, alcohols and a variety of organic chemicals. Symptoms include gas, bloat, heartburn and/or pain in the stomach area, and because of the organic chemicals, there can be headaches, dizziness, lightheadedness, wooziness and post-meal fatigue. To clear intestinal yeast, first the tongue and mouth must be cleansed so yeast does not reenter the system with every swallow. Next, since yeast germs feed on sugars and starches, follow the low carbohydrate diet outlined below. Finally, to replenish the normal, beneficial microbes, eat PLAIN yogurt daily, drink Kefir, 4 ounces daily, and/or take acidophilus, 2 capsules three times daily after meals.

YEAST CONTROL DIET- restricted carbohydrate regimen

UNRESTRICTED FOODS

All protein foods, such as meat, fish, fowl, cheese, eggs, dairy, tofu

RESTRICTED FOODS

FRUITS

Fruits may be a problem because they contain a large amount of sugars. However, if the fruit contains a lot of fiber, this may make up for the sugars to some degree. Thus:

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

EXAMPLES:

ALLOWED IN GENEROUS AMOUNTS

Grapefruit, lemons, limes, tomatoes, avocado

ALLOWED IN SMALL AMOUNTS ONLY! (The high fiber content in these hard, crunchy fruits partially makes up for the carbohydrates)

Pears, apples, strawberries, cantaloupe, etc.

NOT ALLOWED (These soft fruits do not have enough fiber)

Oranges, watermelons, bananas, grapes, etc.

No fruit juices either!

VEGETABLES

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

STARCHES

None!! If it is made from flour- any kind of flour- it is not allowed. (No breads, cereals, cake, etc.)

SWEETENERS

NOT ALLOWED

No sugars at all, and no fructose or corn syrup

ALLOWED (if tolerated)

Stevia (safest), honey, and Splenda,

Aspartame (NutraSweet, Equal) may not be tolerated by some patients

Saccharin products are not recommended

DRINKS

ALLOWED

Water, seltzer, caffeine-free diet sodas, coffee and tea without sugar or caffeine, vegetable juices

NOT ALLOWED

Fruit juices, regular sodas, and any drinks sweetened with sugars or syrups

No Alcohol at all

OTHERS

Do not skip any meals. At least three regular meals daily are needed; a better option is to eat very small portions but have between meal snacks to maintain blood sugar and insulin levels. Bedtime snacks, if taken, must be totally carbohydrate free!

PATIENT INSTRUCTIONS ON TICK BITE PREVENTION AND TICK REMOVAL

HOW TO PROTECT YOURSELF FROM TICK BITES

PROPERTY Remove wood piles, rock walls, and bird feeders as these attract tick-carrying small animals and can increase the risk of acquiring Lyme.

INSECTICIDES: Property should be treated with a product designed to target the rodents that carry ticks- bait boxes and a product called "Damminix" can be used. Use these products in conjunction with liquid or granular insecticides.

LIQUID & GRANULAR PESTICIDES: Products meant for widespread application such as permethrin and its derivatives are preferred. They are available as a liquid concentrate and as granules. If liquid insecticides are used, application should be by fogging, not by coarse sprays. Apply these products in a strip a few feet wide at the perimeter of the lawn at any areas adjacent to woods and underbrush. Also treat any ornamental shrubs near the house that may serve as a habitat for small animals. The best time to apply these products is in late Spring and early Fall. In every case, professional application is recommended.

CLOTHING When wearing long pants, tuck the cuffs into the socks so any ticks that get on shoes or socks will crawl on the outside of the pants and be less likely to bite. Also, light colored clothing should be worn so the ticks will be easier to spot. Smooth materials such as windbreakers are harder for ticks to grab onto and are preferable to knits, etc.

Tick repellents that contain "permethrin" (Permanone, Permakill) are meant to be sprayed onto clothing. Spray the clothes before they're put on, and let them dry first. Do not apply this chemical directly to the skin.

Ticks are very intolerant of being dried out. After being outdoors in an infested area, place clothes in the dryer for a few minutes to kill any ticks that may still be present.

SKIN: Insect repellents that contain "DEET" are somewhat effective when applied to the arms, legs, and around the neck. Do not use any repellent over wide areas of the body as they can be absorbed causing toxicity. Also, it is inadvisable to use a product that contains more than 50% DEET, and 25% concentrations are preferred. Use repellents cautiously on small children, as they are more susceptible to their toxic effects. Be aware that this repellent evaporates quickly and must be reapplied frequently.

Check carefully for ticks not only when you get home but frequently while still outside!

HOW TO REMOVE AN ATTACHED TICK

Using a tweezer (not fingers!), grasp the tick as close to the skin as possible and pull straight out. Then apply an antiseptic. Do not try to irritate them with heat or chemicals, or grasp them by the body, as this may cause the tick to inject more germs into your skin. Tape the tick to a card and record the date and location of the bite. Remember, the sooner the tick is removed, the less likely an infection will result.

APPENDIX

RATIONALE FOR TREATING TICK BITES

Prophylactic antibiotic treatment upon a known tick bite is recommended for those who fit the following categories:

1. People at higher health risk bitten by an unknown type of tick or tick capable of transmitting *Borrelia burgdorferi*, e.g., pregnant women, babies and young children, people with serious health problems, and those who are immunodeficient.
2. Persons bitten in an area highly endemic for Lyme Borreliosis by an unidentified tick or tick capable of transmitting *B. burgdorferi*.
3. Persons bitten by a tick capable of transmitting *B. burgdorferi*, where the tick is engorged, or the attachment duration of the tick is greater than four hours, and/or the tick was improperly removed. This means when the body of the tick is squeezed upon removal, irritated with toxic chemicals in an effort to get it to back out, or disrupted in such a way that its contents were allowed to contact the bite wound. Such practices increase the risk of disease transmission.

4. A patient, when bitten by a known tick, clearly requests oral prophylaxis and understands the risks. This is a case-by-case decision.

The physician cannot rely on a laboratory test or clinical finding at the time of the bite to definitely rule in or rule out Lyme Disease infection, so must use clinical judgment as to whether to use antibiotic prophylaxis. Testing the tick itself for the presence of the spirochete, even with PCR technology, is helpful but not 100% reliable.

An established infection by *B. burgdorferi* can have serious, long-standing or permanent, and painful medical consequences, and be expensive to treat. Since the likelihood of harm arising from prophylactically applied anti-spirochetal antibiotics is low, and since treatment is inexpensive and painless, it follows that the risk-benefit ratio favors tick bite prophylaxis.

SUGGESTED ADDITIONAL READING

Evidence Based Guidelines for the Management of Lyme Disease. The International Lyme and Associated Diseases Society. *Expert Rev. Anti-infect. Ther.* 2(1), Suppl. (2004)

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Gestational Lyme Borreliosis. MacDonald, Alan B. *Rheumatic Diseases Clinics of North America* 15 (4), Nov. 1989. 657-678

Cerebral Malaria. Newton, Charles R. et al. *J. Neurol. Neurosurg. Psychiatry.* 2000. Vol 69, 433-441.

RESOURCES

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