Editors Note: These guidelines are written by Dr. Burrascano, who is regarded as being the grandfather of Lyme disease treatment. Although dated (last revised in 2008) and some of the information may be out of date, many patients and physicians continue to find them useful.

Advanced Topics in Lyme Disease

Diagnostic Hints and Treatment Guidelines for Lyme and Other Tick-Borne Illnesses

by Joseph J. Burrascano, Jr., MD
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DISCLAIMER: The information contained in this article 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.

GENERAL BACKGROUND

WHAT IS LYME DISEASE?

I take a broad view of what Lyme Disease actually is. Traditionally, Lyme is defined as 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. Untreated 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 on 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 s/he is 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.

Steroids and other immunosuppressive medications are absolutely contraindicated in Lyme. This also includes intra-articular steroids.

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 frontline physicians have been seeing for years in real patients.

I must very strongly emphasize that all diagnoses of tick-borne infections remains clinical. 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, many other protozoans can be found in ticks, most likely representing species other than B. microti, yet commercial tests for only B. microti...
and B duncani (Formerly known as 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 (see website for details 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 normalized. To ensure sustained levels, when T3 is prescribed, have it compounded in a time-release form.

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 vasocostriction 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 BORRELLIOsis

Diagnostic hints

Lyme Borreliosis (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 (EM) is diagnostic of Bb infection, but is present in fewer than half. Even if present, it may go unnoticed by the patient.

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.

You should not miss the chance to treat early disease, for this is when the success rate is the highest.

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, be 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 93KD bands are 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.

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

<table>
<thead>
<tr>
<th>Test</th>
<th>Relative Value</th>
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<tbody>
<tr>
<td>Tick exposure in an endemic region</td>
<td>1</td>
</tr>
<tr>
<td>Historical facts and evolution of symptoms over time consistent with Lyme</td>
<td>2</td>
</tr>
<tr>
<td>Systemic signs &amp; symptoms consistent with Bb infection (other potential diagnoses excluded):</td>
<td></td>
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<tr>
<td>Single system, e.g., monoarthritis</td>
<td>1</td>
</tr>
<tr>
<td>Two or more systems, e.g., monoarthritis and facial palsy</td>
<td>2</td>
</tr>
<tr>
<td>Erythema migrans, physician confirmed</td>
<td>7</td>
</tr>
<tr>
<td>Acrodermatitis Chronica Atrophicans, biopsy confirmed</td>
<td>7</td>
</tr>
<tr>
<td>Seropositivity</td>
<td>3</td>
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<tr>
<td>Seroconversion on paired sera</td>
<td>4</td>
</tr>
<tr>
<td>Tissue microscopy, silver stain</td>
<td>3</td>
</tr>
<tr>
<td>Tissue microscopy, monoclonal immunofluorescence</td>
<td>4</td>
</tr>
<tr>
<td>Culture positivity</td>
<td>4</td>
</tr>
<tr>
<td>B. burgdorferi antigen recovery</td>
<td>4</td>
</tr>
<tr>
<td>B. burgdorferi DNA/RNA recovery</td>
<td>4</td>
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</tbody>
</table>

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.
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 |

<table>
<thead>
<tr>
<th>SYMPTOM OR SIGN</th>
<th>CURRENT SEVERITY</th>
<th>CURRENT FREQUENCY</th>
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</thead>
<tbody>
<tr>
<td>Persistent swollen glands</td>
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<tr>
<td>Sore throat</td>
<td>N</td>
<td>MILD</td>
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<tr>
<td>Fevers</td>
<td>Y</td>
<td></td>
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<tr>
<td>Sore soles, esp. in the AM</td>
<td>N</td>
<td></td>
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<tr>
<td>Joint pain</td>
<td></td>
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<tr>
<td>Fingers, toes</td>
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<td></td>
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<tr>
<td>Ankles, wrists</td>
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<td></td>
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<tr>
<td>Knees, elbows</td>
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<td></td>
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<tr>
<td>Hips, shoulders</td>
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<tr>
<td>Joint swelling</td>
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<tr>
<td>Fingers, toes</td>
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<td>Ankles, wrists</td>
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<td>Knees, elbows</td>
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<td></td>
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<tr>
<td>Hips, shoulders</td>
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<tr>
<td>Unexplained back pain</td>
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<tr>
<td>Stiffness of the joints or back</td>
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<tr>
<td>Muscle pain or cramps</td>
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<tr>
<td>Obvious muscle weakness</td>
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<td>Twitching of the face or other muscles</td>
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<td>Confusion, difficulty thinking</td>
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<tr>
<td>Difficulty with concentration, reading, problem absorbing new information</td>
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<tr>
<td>Word search, name block</td>
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<td></td>
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<tr>
<td>Forgetfulness, poor short term memory, poor attention</td>
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<td></td>
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<tr>
<td>Disorientation: getting lost, going to wrong places</td>
<td></td>
<td></td>
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<tr>
<td>Speech errors- wrong word, misspeaking</td>
<td></td>
<td></td>
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<tr>
<td>Mood swings, irritability, depression</td>
<td></td>
<td></td>
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<tr>
<td>Anxiety, panic attacks</td>
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<tr>
<td>Psychosis (hallucinations, delusions, paranoia, bipolar)</td>
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<tr>
<td>Tremor</td>
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<tr>
<td>Seizures</td>
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<tr>
<td>Headache</td>
<td></td>
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<tr>
<td>Light sensitivity</td>
<td></td>
<td></td>
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<tr>
<td>Sound sensitivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vision: double, blurry, floaters</td>
<td></td>
<td></td>
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<tr>
<td>Ear pain</td>
<td></td>
<td></td>
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<tr>
<td>SYMPTOM OR SIGN</td>
<td>CURRENT SEVERITY</td>
<td>CURRENT FREQUENCY</td>
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<td>-----------------------------------------------------</td>
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<tr>
<td>Hearing: buzzing, ringing, decreased hearing</td>
<td>NONE</td>
<td>MILD</td>
</tr>
<tr>
<td>Increased motion sickness, vertigo, spinning</td>
<td></td>
<td>MODERATE</td>
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<tr>
<td>Off balance, “tippy” feeling</td>
<td></td>
<td>SEVERE</td>
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<tr>
<td>Lightheadedness, wooziness, unavoidable need to sit or lie</td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>Tingling, numbness, burning or stabbing sensations, shooting pains, skin hypersensitivity</td>
<td></td>
<td>NEVER</td>
</tr>
<tr>
<td>Facial paralysis-Bell’s Palsy</td>
<td></td>
<td>OCCASIONAL</td>
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<tr>
<td>Dental pain</td>
<td></td>
<td>OFTEN</td>
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<tr>
<td>Neck creaks and cracks, stiffness, neck pain</td>
<td></td>
<td>CONSTANT</td>
</tr>
<tr>
<td>Fatigue, tired, poor stamina</td>
<td></td>
<td></td>
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<tr>
<td>Insomnia, fractionated sleep, early awakening</td>
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<tr>
<td>Excessive night time sleep</td>
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<tr>
<td>Napping during the day</td>
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<tr>
<td>Unexplained weight gain</td>
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<td></td>
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<tr>
<td>Unexplained weight loss</td>
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<td></td>
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<tr>
<td>Unexplained hair loss</td>
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<tr>
<td>Pain in genital area</td>
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<td></td>
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<tr>
<td>Unexplained menstrual irregularity</td>
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<tr>
<td>Unexplained milk production; breast pain</td>
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<td>Low abdominal pain, cramps</td>
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<td>Heart murmur or valve prolapse?</td>
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<td>“Heart block” on EKG</td>
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<td>Breathlessness, “air hunger”, unexplained chronic cough</td>
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<td>Night sweats</td>
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<td>Exaggerated symptoms or worse hangover from alcohol</td>
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<td>Symptom flares every 4 wks.</td>
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LYME DISEASE TREATMENT GUIDELINES

LYME BORRELIOSIS:

Background

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 for 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 L-form), and the recently discovered cystic form (presently, there is controversy whether the cyst is different from the L-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.

BORRELLIA 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 are more effective than 100 mg qd. Likewise, this is why IV doses of 400 mg once a day are 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, peak and trough levels should be measured (for details, refer to the antibiotic dosage table). Because of its short half-life and need for high levels, amoxicillin is usually administered along with probenecid. An extended release formulation of amoxicillin+clavulananate (“Augmentin XR”) may also be considered if adequate trough levels are difficult to attain. An attractive alternative is benzathine penicillin (“Bicillin-LA”- see below). 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 that contains some of the more common skin pathogens in addition to Bb. Because of 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 peak and trough 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 super-infection problems with ceftriaxone can be lessened if this drug is given in interrupted courses (known commonly as “pulse therapy”- refer to chapter on this on page 20), 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 only minimally so 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. So why is it erythromycin is ineffective, and why have initial clinical results with azithromycin (and to a lesser degree, clarithromycin 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.

**METRONIDAZOLE (Flagyl)** When present in a hostile environment, such as a 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 irritating 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 briefer 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 [intravenous] is superior to oral therapy in chronic patients. Options include intramuscular long acting penicillin G (benzathine penicillin, or “Bicillin-LA”) or intravenous antibiotics.

**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 ÷ √ RR interval
- Normals: Females <450 ms, Males < 470 ms
- Want K+ > 4.0, Mg++ > 2.0; avoid hypocalcemia
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.

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. Observations 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 apparent 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 [INTRAVENOUS] 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
**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:

- Adults: oral therapy- must continue until symptom and sign free for at least one month, with a 6 week minimum.
- Children: oral therapy until no active disease for 4 to 8 weeks (4-6 months typical) then oral or IM, if effective, to same endpoint.

**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 to 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.

**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 (i.e. cefotaxime, 12 g daily), increasing efficacy
- More toxic medications can be used with increased safety (i.e.: 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**

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 (i.e: 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 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.

*The author serves on the Board of the International Lyme and Associated Diseases Society (ILADS). This article is excerpted by permission from the Sixteenth Edition of *Advanced Topics in Lyme Disease*, Copyright 2008. Please visit the Dr. Burrascano’s website for complete guidelines and details on co-infections.*

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**Online State Support Groups**

Join with others in your own state to bring change through education, advocacy and activism. Here's how to find your own online state group:

Go to http://health.groups.yahoo.com/group/STATENAMELyme for instructions.

There are groups for each state and Washington DC. There is also a “militarylyme” for service people and a “lyme-espanol” for Spanish speakers.

All the state sites are moderated, mostly by volunteers within the state. They can help you find resources, answer your questions, and let you know about local events. CALDA makes sure the state groups receive action alerts and updates on national issues.

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**Help Spread the Word about Lyme Disease**

**LYME DISEASE**

*A National Health Crisis*

www.lymedisease.org

Lyme Bumper Stickers!

Let's bring awareness to our cause! These bright green bumper stickers are easily removed by just peeling them off. They say, “Lyme Disease, A National Health Crisis.” They are available for a suggested donation of $3 each.

Free shipping with your donation. Items can be ordered at www.LymeDisease.org or send a check to: CALDA, 1026 Mangrove Ave, Suite 10, Chico CA 95926. Need more information? Please contact Marisa at mnayfach@yahoo.com or call her at 415-499-3172.
Perhaps the most important diagnostic concept in Lyme disease is that Lyme is a clinical diagnosis, not a laboratory one. Yet this very concept seems to be one of the hardest for patients and physicians to truly grasp. While I don’t know why this is the case, here are my thoughts on the matter.

Most cases of late Lyme are not diagnosed right off the bat. Several studies have shown that patients usually see multiple physicians before being diagnosed and delays in diagnosis are often greater than a year. Those delays, to put it bluntly, represent physician error. It is not surprising then, that patients might question a clinical diagnosis of Lyme without “proof” in the form of a test result. Busy physicians, with little experience in late Lyme disease, may find it difficult to reach a clinical diagnosis. Patients present in a myriad of ways and the variety defies clinical logic; how could a single infectious agent cause such divergent symptoms? Colleagues may quibble over which part of a history is most important or disagree with exam findings but it’s hard for them to argue with a lab result. Plus, it’s easier to take a two-minute history and order a blood test then it is to do a complete review of systems in a patient who has many, many symptoms. So physicians, too, want proof.

Enter lab testing. Everybody wants it, and the CDC won’t recognize late Lyme without it, but what are they getting and, if they looked a little closer, would they still want it? Before getting into the specifics of Lyme disease testing, a review of some basic lab principles is in order.

### Sensitivity and Specificity

When people talk about testing of any sort, one question that always comes up is, “Is the test accurate?” People want to know that the result is a true one, that it’s right. Accuracy in lab testing is determined by a test’s sensitivity and specificity. The ideal test would identify every patient who has the illness being tested for yet not indicate a patient had the disease when they don’t. There are precious few ideal tests.

This grid shows the relationship between a disease and its test.

<table>
<thead>
<tr>
<th>Disease Positive</th>
<th>Disease Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Positive</td>
<td>True Positive</td>
</tr>
<tr>
<td>Test Negative</td>
<td>False Positive</td>
</tr>
<tr>
<td>False Negative</td>
<td>True Negative</td>
</tr>
</tbody>
</table>
**Sensitivity** is the ability of a test to find all of the ill. It can be expressed as:

\[
\text{Sensitivity} = \frac{\text{True Positives}}{\text{True Positives} + \text{False Negatives}}
\]

From the perspective of sensitivity, false negatives are a bad thing. When dealing with a significant illness we don’t want to tell a patient they don’t have the disease (and don’t need treatment) when they do.

**Specificity** is the ability of a test to only identify those who are ill. It can be expressed as:

\[
\text{Specificity} = \frac{\text{True Negatives}}{\text{True Negatives} + \text{False Positives}}
\]

From the perspective of specificity, false positives are a bad thing. We don’t want to tell people they have a condition that requires treatment when they don’t.

Sensitivity and specificity to not go hand-in-hand, in fact they vary inversely with each other. A highly sensitive test will have few false negative results but is likely to have several false positives. A highly specific test will have few false positives but it also yields many false negatives.

Most lab tests are not reported as being simply positive or negative but rather give a specific value. By manipulating the “normal” cut-off point for a test you can increase its sensitivity or specificity. But increasing the value of one comes at the cost of the other.

If failure to identify a condition leads to significant consequences and treating it is safe and easy you would be willing to sacrifice specificity to gain sensitivity. But if a disease is nonfatal and the treatment kills those who receive it when they don’t have the disease then you would desire a highly specific test.

There are situations where you want to identify all patients who have an illness while at the same time treating only those who truly have it. Here it makes sense to run a sequence of tests. The first test should be highly sensitive so that you will have very few false negatives. In doing this you will pick up some false positives so the second test (run only on those who were positive on test 1) should be highly specific, finding only those who truly have the illness. If you mistakenly reversed the order of these tests the result would be disastrous.

### Applying this to serologic testing for Lyme disease

The earlier that Lyme is diagnosed, the easier it is to treat. Missing the diagnosis can lead to significant morbidity so it is important that all potential Lyme patients be identified; to do this we want a highly sensitive test. Yet, the inappropriate use of antibiotics can also be harmful so it is important to only treat patients who have Lyme; here we would want a very specific test. Thus, Lyme is an illness where sequential testing makes sense and that’s the reason for the CDC’s two-tier protocol.

What looks good in theory falls apart in practice. This happens because the first step in the protocol lacks sufficient sensitivity. Most patients are first tested with the C6 ELISA by Immunetics, Inc. The following appears in the CDC’s publication entitled Laboratory Management of Lyme disease Using a C6 Peptide Based ELISA Assay.

> “The diagnosis of Lyme disease is based on clinical symptoms including potential exposure in a tick habitat and laboratory testing. Clinical symptoms include EM or a late stage manifestation of Lyme. EM appears in only 60-80% of infected patients. Laboratory diagnosis utilizes a two-tier protocol recommended in 1994 by the CDC and other groups. In 1999 a novel peptide based assay for Lyme was first published using a 26 amino acid peptide (C6) which was determined to be conserved and immunodominant. In a 2003 study by the CDC comparing a C-6 peptide ELISA assay to the two-tiered testing protocol using a whole cell lysate ELISA and the western blot confirmatory test, showed, “overall sensitivities for detecting IgG antibodies to VlsE1 or C6 in samples from patients with diverse manifestations of Lyme disease were equivalent to that of 2-tiered testing.” Data presented in the CDC paper showed that the sensitivity of the two tiered protocol for Acute Lyme (EM and early disseminated) was 38% (62% false negatives) while for the C6 assay alone the sensitivity was 44% (56% false negatives). For early convalescent patients, sensitivity was 65% for the two-tie method and 70% for the C6 ELISA method. Clearly the single C6 Assay stands as equal to the two-tier test protocol in performance while improving significantly on cost per test turn around time and simplicity of testing.”

Look again at the sensitivity and specificity numbers. In a paper by Bacon et al, C6 could obtain a sensitivity of only 70%. This is a far cry from the sensitivity values we need to have in the first test of a two-step sequence and I suspect it’s much lower than you were led to believe. When this test first hit the market the company claimed it had sensitivities close to 100% but that didn’t pan out in real patients. Several papers have looked into why this happened and much of it comes down to differences between Borrelia burgdorferi species and strains and differences between the specimens used to develop the test and the specimens obtained from typical patients.

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**Note:** The text contains scientific terms and references that are essential for a comprehensive understanding of the subject matter. It is recommended to consult scientific journals and authoritative sources for more detailed and accurate information. The provided references are not included here for brevity, but they are crucial for validating the statements made in the text.
Since step 1 is not sensitive enough, missing 30 – 56% of patients tested, it seems best to go back to making the diagnosis on clinical grounds. A physician may decide to use a positive result as a confirmatory test but given the poor sensitivity, a negative test has little value; it certainly does not rule out the infection.

If you decide to do serologic testing anyway, it makes sense to skip the ELISA. That’s because a negative test has no usefulness and a positive test requires a confirmatory western blot. The sensitivity of western blots is dependent on the source of the test. There are pre-made kits with variable sensitivity and there are some specialized labs which do theirs tests from scratch. Either way, the sensitivity remains low, generally no more than 65%. If you do skip the ELISA and order a western blot, make it clear to your lab personnel that this is what you want. Many labs have an automatic over-ride for Lyme testing. This means that when you order a western blot they start with the ELISA anyway and cancel the western blot if the ELISA is negative. Some physician orders apparently don’t count for much; make sure yours do.

Most labs use FDA-licensed kits for doing western blots. This is because the test is very labor-dependent. Using a kit cuts down on the work but a lab tech still needs to “read” the bands and grade them based on the intensity of the signal. That is a subjective measure and it is reasonable to assume that techs who read lots of blots are better at it than those who rarely read them. When using a kit, a lab tech can only comment on the 10 CDC-designated bands. Even if a *Borrelia burgdorferi*-specific band were present, such as 31 or 34, the physician would not be notified of the occurrence. Labs which perform their western blots from scratch are free to report on any band that shows up. To create their own in-house western blot, a lab must jump through several regulatory hoops to prove that their tests are valid. To me it’s like baking a cake – Betty Crocker might be quicker and easier but cakes made from scratch do taste better.

As stated above, western blots are insufficiently sensitive but they are highly specific, usually 95% or greater. Therefore a positive result truly does confirm a clinical diagnosis. One always has to keep in mind that western blots may remain positive after treatment. In asymptomatic patients you would expect them to eventually be clear of antibodies but we don’t know when that event occurs in an individual patient. In symptomatic patients, it would seem prudent to consider a positive western blot as a sign of ongoing infection.

The sensitivity and specificity of western blots can be manipulated by changing the band criteria for what constitutes a positive test. The criteria adopted by the CDC were chosen on the basis of specificity. Recall that these were supposed to be criteria for establishing a surveillance group of Lyme patients. Surveillance groups are very select – every effort is made not to include someone in the group who does not have the illness. Epidemiologists want to follow an illness over time and geographic region and by treatment outcome; surveillance groups make this possible. But a patient can still have Lyme without meeting surveillance diagnostic criteria. Failing to recognize this possibility has been a common mistake made by most clinicians across the country.

To summarize: current ELISA tests, including the C6, are too insensitive to be used as a step 1 test in a sequential test scheme. Western blots have low sensitivity but high specificity. There is no compelling reason to deviate from the previously held position which acknowledged that Lyme disease should be diagnosed on clinical grounds.

References


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