Lyme Disease: IV Antibiotic Therapy

Policy

Over diagnosis and overtreatment of Lyme disease is common due to its nonspecific symptoms, a lack of standardization of serologic tests, and difficulties in interpreting serologic test results. Lyme disease is a multisystem inflammatory disease caused by the spirochete Borrelia burgdorferi and transmitted by the bite of an infected ixodid tic. The disease is characterized by stages, beginning with localized infection of the skin (erythema migrans), followed by dissemination to many sites.

Manifestations of early disseminated disease may include lymphocytic meningitis, facial palsy, painful radiculoneuritis, atrioventricular nodal block, or migratory musculoskeletal pain. Months to years later, the disease may be manifested by intermittent oligoarthritis; particularly involving the knee joint, chronic encephalopathy, spinal pain, or distal paraesthesia. While most manifestations of Lyme disease can be adequately treated with oral antibiotics, intravenous (IV) antibiotics are indicated in some patients with neurologic involvement or atrioventricular heart block. However,

In particular, patients with chronic fatigue syndrome or fibromyalgia are commonly misdiagnosed as possibly having Lyme disease and undergo inappropriate IV antibiotic therapy. The purpose of this policy is to provide diagnostic criteria for the appropriate use of IV antibiotic therapy. The following paragraphs describe the various manifestations of Lyme disease that may prompt therapy with IV antibiotics and the various laboratory tests that are used to support the diagnosis of Lyme disease.

GEHA considers outpatient intravenous antibiotic therapy medically necessary in adult and pediatric members with the diagnosis of Lyme disease only when it is based on the clinical presentation of signs and symptoms compatible with the disease and supported by a positive serologic and/or cerebrospinal fluid (CSF) titer by indirect immunofluorescence assay (IFA), Prevue Borrelia burgdorferi antibody detection assay, or enzyme-linked immunosorbent assay (ELISA), which itself is validated by a positive Western Blot Test (see CDC criteria in note* below).

Once a definitive diagnosis of Lyme disease is established, GEHA considers an initial 4-week course of outpatient intravenous antibiotic therapy medically necessary when any of the following conditions is met:

- Lyme arthritis that persists after failing to respond to a 4-week course of appropriate oral antibiotic therapy
  - Moderate to severe cardiac involvement as evidenced by any of the following:
    - A 1st-degree heart block with P-R interval greater than 0.4 seconds
    - Congestive heart failure
    - My pericarditis
• Neurologic involvement of Lyme disease (neuroborreliosis) as evidenced by any of the following:
  o Encephalopathy/encephalomyelitis
  o Meningitis confirmed by CSF analysis showing a lymphocytic pleocytosis with evidence of antibody production against Borrelia burgdorferi in the CSF
  o Sensory/motor radiculoneuropathy or peripheral neuropathy (weakness and/or pain in the extremities or chest)

• All cases of Lyme disease in pregnant women who exhibit symptoms and signs of any of the following:
  o Stage II Lyme disease with early dissemination documented by organ-specific manifestations of infection (arthritic, cardiac, or neurologic)
  o Stage III late Lyme disease documented by findings of arthritis and/or neurologic complications, such as encephalomyelitis and subacute encephalitis

GEHA considers initial intravenous antibiotic therapy experimental and investigational for the following indications, because the benefit of intravenous antibiotic therapy for these indications has not been established:

• Early Lyme disease or new-onset Lyme arthritis

• Flu-like syndrome (fatigue, fever, headache, mildly stiff neck, arthralgia, and myalgias)

• Non-specific subjective symptoms, such as persistent, chronically debilitating fatigue (chronic fatigue syndrome), difficulty in concentrating, musculoskeletal pain (fibromyalgia), and headache

• Prophylaxis in a person who is asymptomatic and the only evidence for Lyme disease is a positive immunologic test (ELISA, IFA, or Western blot)

• Mild cardiac involvement of Lyme disease as evidenced by any of the following:
  ▪ 1st-degree heart block with P-R interval less than 0.4 seconds
  ▪ Left ventricular dysfunction without congestive heart failure
  ▪ Transient ST-T depression, T-wave changes

• Isolated manifestations of neurologic involvement of Lyme disease (such as Bell's facial nerve palsy/paralysis)

• Pregnant woman presenting with localized Lyme disease manifested as a single lesion of erythema migrans without any other symptoms suggestive of disseminated disease

• Minor neurologic manifestations of Lyme disease (including headache, stiff neck, and irritability).
GEHA considers the following diagnostic tests for Lyme disease experimental and investigational because there is inadequate scientific evidence to prove their usefulness in clinical practice:

- Antigen detection
- Borrelia burgdorferi antibody index testing
- Borrelia culture
- C6 peptide ELISA assay (using recombinant VlsE1 or peptide antigens of Borrelia burgdorferi)
- CD57+ lymphocyte counts
- Chemokine CXCL13
- Complement split products (e.g., C3a and C4a)
- Cyst formation
- Cytokine analysis
- Immune complexes
- iSpot Lyme assay
- Lymphocyte markers
- Lymphocyte transformation test
- Measurement of natural killer (NK) cells
- Microscope-based assays
- Neuroadrenal expanded panel (including histamine, serotonin, and hydroxyindoleacetic acid)
- Polymerase chain reaction (PCR) for identification or quantification of Lyme disease (B. burgdorferi) spirochetal DNA or RNA
- Positron emission tomography (PET) scanning
- Provocative testing (testing for B. burgdorferi after antibiotic provocation)
- Serum borreliacidal assay
- SPECT scanning
- T-cell proliferation response assay
- Urine antigen assay
- Xenodiagnosis

GEHA considers scheduled repeated testing for Lyme disease in a member without a change in signs and symptoms not medically necessary.

- GEHA considers one repeat 4-week course of outpatient intravenous antibiotic therapy medically necessary when the member meets all of the following criteria:
  - The member has met the criteria for an initial course of intravenous antibiotic therapy, using lab results obtained within the past 3 months; and
  - The member has completed an initial course of appropriate intravenous antibiotic therapy; and
The member has objective evidence of either relapse of infection, progression of Lyme disease organ damage, and/or the finding of a new focus or type of organ damage.

- **GEHA considers additional antibiotic therapy in post-treatment, persistently fatigued patients (post-Lyme disease syndrome) experimental and investigational because intravenous antibiotic therapy has not been shown to be effective for this indication.**

- **Concurrent Babesiosis or cat-scratch disease is not, in and of itself, considered a medically necessary indication for long-term intravenous antibiotic therapy for Lyme disease. Long-term intravenous antibiotic therapy is generally not medically necessary in immunocompetent persons with Bartonella-associated vasculo-proliferative diseases (bacillary angiomatosis-peliosis and verruga peruana) or Bartonella bacteremia (other than Bartonella endocarditis). Intravenous antibiotic therapy may be medically necessary in persons with severe Bartonella infection, immunocompromised persons, and systemic Bartonella infection complicated by bony or parenchymal involvement or endocarditis.**

- **GEHA considers hyperbaric oxygen therapy experimental and investigational for the treatment of Lyme disease because its effectiveness for this indication has not been established:**

- **GEHA considers intravenous antibiotic therapy experimental and investigational for the treatment of Q fever because its effectiveness over oral antibiotics for this indication has not been established.**

- **GEHA considers testing ticks for Borrelia burgdorferi experimental and investigational because it has not been proven to be useful for deciding if a person should receive medical treatment following a tick bite.**

- **GEHA considers singlet oxygen therapy experimental and investigational for the treatment of Lyme disease because of a lack of evidence regarding its effectiveness.**

- **GEHA considers chelation therapy experimental and investigational for the treatment of Lyme disease because of a lack of evidence regarding its effectiveness.**

- **GEHA considers intravenous ascorbic acid or intravenous magnesium experimental and investigational for the treatment of Lyme disease because of a lack of evidence regarding their effectiveness.**

- **GEHA considers the use of alpha lipoic acid or “Healing Detox Drips” for the treatment of Lyme disease experimental and investigational because of insufficient evidence of its effectiveness.**
• *Note: According to the CDC (1995), the recommended method for serologic detection of active disease or previous infection involves a 2-test approach using a sensitive enzyme immunoassay (EIA) or IFA followed by a Western immunoblot. All specimens positive or equivocal by a sensitive EIA or IFA should be tested by a standardized Western immunoblot.

• The CDC (1995) states that when Western immunoblot is used during the first 4 weeks of disease onset (early LD), both immunoglobulin M (IgM) and immunoglobulin G (IgG) procedures should be performed. However, a positive IgM immunoblot alone is not considered sufficient evidence of active disease in a person with Lyme disease of more than 1 month’s duration. Although the presence of IgM antibodies is useful in evaluating early disease, the CDC states that a positive IgM test result alone is not recommended for use in determining active disease in persons with illness greater than 1 month’s duration because the likelihood of a false-positive test result for a current infection is high for these persons. The following criteria for a positive Western Blot are adapted from the CDC (1995):
  o IgM immunoblot -- 2 of the following bands are present:
    o 21/22/23/24 kDa (OspC)*
    o 39 kDa (BmpA)
    o 41 kDa ( Fla).
    o or
  o IgG immunoblot -- 5 of the following bands are present:
    o 18 kDa
    o 21/22/23/24 kDa (OspC)*
    o 28 kDa
    o 30 kDa
    o 39 kDa (BmpA)
    o 41 kDa ( Fla)
    o 45 kDa
    o 58 kDa (not GroEL)
    o 66 kDa
    o 93 kDa.

• A positive serology, on its own, is not considered a medically necessary indication for antibiotic therapy for Lyme disease. According to the CDC, positive antibody tests should be correlated with symptoms to be clinically meaningful. According to the CDC (1995), if an individual with suspected early Lyme disease has a negative serology, serologic evidence of infection is best obtained by testing of paired acute- and convalescent-phase serum samples. Serum samples from persons with disseminated or late-stage Lyme disease almost always have a strong IgG response to Borrelia burgdorferi antigens.

• The apparent molecular mass of outer surface protein C (OspC) is strain-dependent; thus the 21 kDa, 22 kDa, 23 kDa, and 24 kDa proteins referred to above are the same.
Rationale

The use and duration of intravenous antibiotic therapy in Lyme disease (LD) remains controversial. Researchers are currently conducting studies to assess the optimal duration of antibiotic therapy for the various manifestations of LD. In some areas of the country, patients are being treated for months to 1 year or more with daily parenteral or oral antibiotics. In a randomized controlled study, Wormser et al. (2003) stated that treatment of patients with early LD has trended toward longer duration despite the absence of supporting clinical trials. These investigators concluded that extending treatment with doxycycline from 10 to 20 days or adding 1 dose of ceftriaxone to the beginning of a 10-day course of doxycycline did not enhance therapeutic efficacy in patients with erythema migrans. Regardless of regimen, objective evidence of treatment failure was extremely rare.

In the largest long-term study of outcomes based on treatment duration in patients with early LD, Kowalski et al. (2010) found that patients treated for 10 days with antibiotic therapy for early LD have long-term outcomes similar to those of patients treated with longer courses. The investigators found that treatment failure after appropriately targeted short-course therapy, if it occurs, is exceedingly rare. Kowalski reported on the long-term clinical outcomes of patients with early localized and early disseminated LD based on the duration of antibiotic therapy prescribed. Although these 6 patients met a priori treatment failure criteria, 4 of these patients' clinical details suggested re-infection, 1 was treated with an inappropriate antibiotic, and 1 developed facial palsy early in therapy. Re-infection developed in 4% of patients. The 2-year treatment failure-free survival rates of patients treated with antibiotics for 10 days, 11 to 15 days, or 16 days were 99.0%, 98.9%, and 99.2%, respectively. Multiple measures of long-term function -- including pain, general health, and emotional and physical well-being -- were similar among groups. The only statistically significant difference was decreased social functioning in the group of patients with the longest treatment duration.

Randomized controlled studies of treatment of patients who remain unwell after standard courses of antibiotic therapy for LD have shown that repeated or prolonged courses of antibiotic therapy are not effective for such patients. Krupp et al. (2003) reported that ceftriaxone therapy in patients with post-Lyme syndrome (PLS) with severe fatigue was associated with an improvement in


fatigue but not with cognitive function or an experimental laboratory measure of infection. Because fatigue (a non-specific symptom) was the only outcome that improved and because treatment was associated with adverse events, these authors concluded that their findings did not support the use of additional antibiotic therapy with intravenous ceftriaxone in post-treatment, persistently fatigued patients with PLS. This in agreement with the findings of Kaplan et al (2003) who concluded that patients with post-treatment chronic Lyme disease who have symptoms (e.g., fatigue, depression) but show no evidence of persisting Borrelia infection do not show objective evidence of cognitive impairment. Additional antibiotic therapy was not more beneficial than administering placebo. Added expense and toxicity are the only proven results of such practice. Iatrogenic problems, such as gallbladder disease, fungal infections, and other superinfections, and gastrointestinal problems, certainly increase with prolonged use of broad-spectrum antibiotics. This highlights the need for an appropriate diagnosis before subjecting the patient to antibiotic regimens.

In a randomized, controlled clinical trial, a prolonged course of antibiotics produced no sustained benefit in persons with Lyme encephalopathy. Fallon et al (2008) reported on a randomized, placebo-controlled trial assessing the efficacy of a 10-week course of intravenous ceftriaxone in patients with a history of clinical LD, as well as current serologic evidence of Borrelia burgdorferi infection, greater than 3 weeks of previous intravenous ceftriaxone therapy completed greater than 4 months before study entry, and objective evidence of memory impairment. A total of 37 patients with Lyme encephalopathy (out of 3,368 individuals who were screened) were enrolled. Additionally, 20 healthy control subjects were included to correct for practice effects from repeated neurocognitive testing. Neuropsychological testing) was conducted at baseline and at weeks 12 and 24 after study entry. At 12 weeks, ceftriaxone recipients showed better cognitive improvement than did placebo recipients (on an aggregate analysis, although not in any single domain. However, this benefit was not present at 24 weeks. No benefits were noted on concurrent rheumatologic assessments. Adverse events related to the study drug or the catheter were seen in 6 of 23 ceftriaxone recipients (26.1 %) and in 1 of 14 placebo recipients (7.1 %). Commenting on this study, Ellison (2007) said that "[t]he findings that ceftriaxone therapy was not significantly better than placebo, that any benefit was short lived, and


6 Ellison RT. Antibiotics for Lyme encephalopathy? In a randomized, controlled trial, ceftriaxone produced no sustained benefit. Journal Watch Infectious Diseases, October 31, 2007.
that the drug was associated with frequent adverse effects would seem to close the door on any such treatment for Lyme encephalopathy."

The Infectious Diseases Society of America (Wormser et al, 2006) has concluded that there is no scientific evidence to support the need for multiple or very prolonged courses of antibiotics in LD, and that such treatments may cause serious and even fatal adverse effects.

Pfister and Rupprecht (2006) noted that the diagnostic criteria of active neuroborreliosis include inflammatory changes of the cerebrospinal fluid (CSF) and an elevated specific Borrelia CSF-to-serum antibody index, indicating intrathecal Borrelia antibody production. Patients with neuroborreliosis are usually treated with intravenous ceftriaxone for 2 to 3 weeks. In case of allergy, doxycycline may be used. Treatment efficacy is detected by the improvement of the neurological symptoms and the normalization of the CSF pleocytosis. The measurement of serum and CSF antibodies is not suitable for follow-up, because they frequently persist. Post-Lyme disease (PLD) syndrome is characterized by persistent complaints and symptoms after previous treatment for Lyme borreliosis, e.g., musculoskeletal or radicular pain, dysaesthesia, and neurocognitive symptoms that are often associated with fatigue. There is no formal definition of the PLD syndrome, and its pathogenesis is unclear. Recent controlled studies do not support the use of additional antibiotics in these patients, but recommend primarily symptomatic strategies. Moreover, Feder et al (2006) stated that antibiotic therapy for more than 8 weeks for patients with LD is not indicated. Chronic LD due to antibiotic resistant infection has not been demonstrated.

The diagnosis of LD is valid only in a person with erythema migrans in early LD or for later stages of infection, in a person with a least 1 late manifestation and laboratory confirmation of infection. Laboratory support of the diagnosis of LD requires detection of specific antibodies to this tick-borne spirochete Borrelia burgdorferi in the serum, either by indirect immunofluorescence assay (IFA) or enzyme-linked immunosorbant assay (ELISA), with the latter now preferred because it is more sensitive and specific. A Western blot assay that can detect both IgM and IgG antibodies is used to confirm the diagnosis. Specific IgM antibodies appear first, usually 3 to 4 weeks after the infection begins, while specific IgG antibodies usually appear 6 to 8 weeks after the onset. An elevated IgM is a value greater than 7


than 250 mg/dL and an elevated IgG is a value greater than 1,500 mg/dL. After peaking, these antibodies subsequently decline after 4 to 6 months of illness. The critical issue with these antibody tests is that they must be correlated with the timing of the patient’s symptoms. On their own, they are meaningless.

Recent studies have suggested that the C6 ELISA assay, based on a peptide (C6) that reproduces the sequence of invariable region 6 of VlsE, the antigenic variation protein of *Borrelia burgdorferi*, may improve the sensitivity and standardization of immunoblots for the serologic diagnosis of LD (Marques et al, 2002; Bacon et al, 2003). In this regard, Wilske (2003) stated that it appears promising to use recombinant proteins (DbpA, VlsE, others) or synthetic peptides (the conserved C6 peptide derived from VlsE) as ELISA antigens for the diagnosis of LD. However, a recent randomized controlled study reported that C(6) antibody can not be used to assess treatment outcome or the presence of active infection in patients with PLS (Fleming et al, 2004).

The diagnosis of Lyme neuroborreliosis must be validated with evidence of antibody production against *Borrelia burgdorferi* in the CSF, shown by a higher titer of antibody in the CSF than in the serum. The most helpful CSF test is intrathecal production of specific antibodies. This test is run on paired CSF and serum samples and distinguishes intrathecal antibody production from a positive CSF titer due to serum leakage. A ratio of CSF to serum antibody of greater than 1.0 suggests local central nervous system antibody production and the presence of neuroborreliosis. With rare exceptions, a positive test documents central nervous system (CNS) invasion by *B. burgdorferi*. Other CSF findings suggestive of LD include mild mononuclear pleocytosis and protein elevation. Studies that are normal or negative include the CSF glucose level, VDRL, and myelin basic protein. In North American Lyme patients, CSF oligoclonal bands and increased IgG index (very common findings in multiple sclerosis) are unusual. There are a number of experimental CSF tests that look promising (Borrelia-specific immune complexes, polymerase chain reaction [PCR], antigen detection), but they are available only at a few research centers and have not been validated.

According to evidence-based guidelines, PCR of *B. burgdorferi* DNA or RNA has not been validated for either the diagnosis of LD or monitoring response to therapy. Polymerase chain reaction remains a research technique, in part because PCR can become easily contaminated, producing false-positive results. In addition, no large clinical series have been reported that assess the performance of the test in the non-research setting. American College of Physicians - American Society of Internal Medicine (ACP-ASIM) guidelines on diagnosis of LD (1997) state that PCR of serum or CSF “need[s] further validation” and that “[p]ublished experience with these techniques [PCR] is insufficient to allow development of guidelines for their use.” The Centers for Disease Control and Prevention (2001) states

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that “PCR has not been standardized for routine diagnosis of Lyme Disease.” The National Institute of Arthritis and Infectious Disease (2001) has explained the reasons why PCR has limited utility in the diagnosis of LD: "To be sure, the polymerase chain reaction (PCR) is an extremely sensitive laboratory test that is capable of detecting very few molecules of bacterial DNA. However, the numbers of Borrelia likely to be present -- if at all -- in patients suspected of having Lyme disease are too small to generate sufficient amounts of bacterial DNA to be detected by this procedure."

Guidelines on treatment of LD from the Infectious Diseases Society of America (Wormser et al\textsuperscript{11}, 2000) do not state any role for PCR in monitoring the treatment of patients with LD. The American Academy of Pediatrics Committee on Infectious Diseases (2003) stated: "New, more sensitive and more specific diagnostic tests, such as the polymerase chain reaction assay, which may be able to identify the presence of even small quantities of spirochetal DNA, are in development. However, physicians should be cautious when interpreting results of these investigational tests until their clinical usefulness has been proven." More recently, the American Academy of Pediatrics Committee on Infectious Diseases (2006) stated that PCR has "no role in diagnosis" of LD.

\textit{Persistence of }B. \textit{burgdorferi} \textit{sero-reactivity long after LD treatment and cure has led to excesses in therapy and attendant drug- and intravenous line-related morbidity, based on the mistaken assumption that persisting sero-positivity equates with persisting infection. Laboratory tests should be employed as an adjunct in the diagnosis of LD, used only when specific symptoms suggest substantial likelihood that the disease is present. Testing as a screening tool should be discouraged.}

An incorrect diagnosis of LD is often made, despite negative test results and the absence of findings suggesting LD, because the patient had symptoms compatible with LD. Some clinicians consider LD a diagnosis of exclusion, and associate any illness compatible with LD as LD. Because these patients are rarely, if ever, cured by antibiotics, this practice has contributed to an epidemic of anxiety about the chronicity of LD. The diagnosis is often supposedly confirmed by transient improvement after therapy. Oral therapy has been shown to elicit placebo responses in as many as 35 \% of patients undergoing oral antibiotic therapy, and rates for intravenous therapy might even be higher.

According to the American Academy of Pediatrics Committee on Infectious Diseases (2006): "The widespread practice of ordering serologic tests for patients with nonspecific symptoms such as fatigue or arthralgia who have a low probability of having Lyme disease is not recommended. Almost all positive serologic test results in these patients are false-positive results. Patients with acute Lyme disease almost always have objective signs of infection (e.g., erythema migrans, facial nerve palsy, \textsuperscript{11}Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and Babesiosis: Clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2006;43(9):1089-1134.}
Nonspecific symptoms commonly accompany these specific signs but are almost never the only evidence of Lyme disease."

An incorrect diagnosis of LD can also be made even in the presence of a positive antibody test. Positive antibody tests are meaningless if not correlated with the duration of the patient's symptoms. In some instances, patients will be tested repeatedly for Lyme antibodies, until inevitably a false positive result will occur, which is then inappropriately interpreted as evidence of LD and used as justification for prolonged antibiotic therapy. The degree of clinical response associated with parenteral antibiotic treatment or decreasing serum titers do not correlate with antibiotic success and should not be used as a guide or reason for extended antibiotic administration. In general, symptoms that persist beyond a full course of parenteral antibiotic therapy generally are not due to continued infection and may actually indicate that the diagnosis is something other than LD.

An editorial summarizing the controversy surrounding the diagnosis and treatment of LD published in the New England Journal of Medicine by the Ad Hoc International Lyme Disease Group (Feder et al, 2007) systematically refuted the arguments behind the diagnosis and treatment of so-called chronic LD. The Ad Hoc Group stated "[c]hronic Lyme disease is the latest in a series of syndromes that have been postulated in an attempt to attribute medically unexplained symptoms to particular infections. Other examples that have now lost credibility are 'chronic candida syndrome' and 'chronic Epstein–Barr virus infection.' The assumption that chronic, subjective symptoms are caused by persistent infection with B. burgdorferi is not supported by carefully conducted laboratory studies or by controlled treatment trials. Chronic Lyme disease, which is equated with chronic B. burgdorferi infection, is a misnomer, and the use of prolonged, dangerous, and expensive antibiotic treatments for it is not warranted."

Whereas early LD, late LD, and PLD symptoms/syndrome are recognized conditions, the term "chronic LD" has recently been popularized by a small number of practitioners (Feder et al, 2007; Chang, 2007). Chronic, non-specific symptoms (e.g., fatigue, headache, dizziness) are attributed to persistent or incurable B. burgdorferi infection, and patients are subsequently treated with long-term parenteral antibiotics.

Objective manifestations of LD include erythema migrans (the most common presentation of early Lyme disease), certain neurologic and cardiac manifestations, and pauciarticular arthritis (the most common presentation of late LD) (Chang, 2007; Feder et al, 2007). These symptoms respond well to conventional antibiotic therapy. Symptoms of PLD include fatigue, musculoskeletal pain, and difficulties with concentration or short-term memory following resolution of objective manifestations of

infection. These symptoms are usually mild, typically resolve within months, and antibiotic therapy is not indicated; when the difficulties persist longer than 6 months, the condition is termed PLD syndrome. Laboratory testing (usually acute- and convalescent-phase serologies) is a key component of LD diagnosis; in most cases, the testing allows clinicians to confirm evidence of current or past *B. burgdorferi* infection (Chang, 2007; Feder et al, 2007).

By contrast, chronic LD is the term assigned to patients reporting chronic symptoms without objective clinical, laboratory, or epidemiologic criteria for infection (Chang, 2007; Feder et al, 2007). They receive chronic parenteral antibiotic therapy for periods of many months to years, despite the absence of any scientific evidence to support this practice.

The Ad Hoc International Lyme Disease Group (Feder et al, 2007) states that chronic antibiotic therapy for chronic LD has resulted in life-threatening anaphylaxis, cholecystectomy after biliary complications from ceftriaxone administration, a fatality due to candidemia from intravenous catheter infection, and other serious adverse events related to intravenous catheters.

The American Academy of Neurology (AAN)'s practice parameter on treatment of nervous system LD (Halperin et al, 2007) provided evidence-based recommendations on the treatment of nervous system LD and PLS. Three questions were addressed: (i) which anti-microbial agents are effective? (ii) are different regimens preferred for different manifestations of nervous system LD? and (iii) what duration of therapy is needed? These investigators analyzed published studies (1983 to 2003) using a structured review process to classify the evidence related to the questions posed. The panel reviewed 353 abstracts; yielding 112 potentially relevant articles that were reviewed, from which 37 articles were identified that were included in the analysis. The authors concluded that there are sufficient data to conclude that, in both adults and children, this nervous system infection responds well to penicillin, ceftriaxone, cefotaxime, and doxycycline (Level B recommendation). Although most studies have used parenteral regimens for neuroborreliosis, several European studies support use of oral doxycycline in adults with meningitis, cranial neuritis, and radiculitis (Level B), reserving parenteral regimens for patients with parenchymal CNS involvement, other severe neurological symptomatology, or failure to respond to oral regimens. The number of children (greater than or equal to 8 years of age) enrolled in rigorous studies of oral versus parenteral regimens has been smaller, making conclusions less statistically compelling. However, all available data indicate results are comparable to those observed in adults. In contrast, there is no compelling evidence that prolonged treatment with antibiotics has any beneficial effect in post-Lyme syndrome.
Roos\textsuperscript{14}(2007) provided the following comment on (AAN)'s practice parameter on treatment of nervous system LD (Halperin et al\textsuperscript{15}, 2007): "Misunderstanding of Lyme disease has created a demand by patients with pain, fatigue, and perceived cognitive trouble to seek prolonged parenteral treatment for Lyme disease and "post-Lyme syndrome." This study provides evidence-based recommendations for appropriate types and duration of antimicrobial therapy for neurologic Lyme disease. It also provides reassurance that the disease can be treated and highlights the lack of evidence that post-Lyme syndrome is due to active \textit{B. burgdorferi} infection that would require prolonged antibiotic therapy."

Testing ticks for \textit{Borrelia burgdorferi} has not been proven to be useful for deciding if a person should receive medical treatment following a tick bite. The Centers for Disease Control and Prevention (CDC, 2005) stated that "In general, the identification and testing of individual ticks is not useful for deciding if a persons should get antibiotics following a tick bite". The California Department of Health Services does not recommend that ticks be tested to determine if treatment is necessary because (i) testing methods vary in accuracy, (ii) the need for treatment should not be based on these test results, and (iii) tick testing results do not necessarily predict if the person bitten will get Lyme disease. Even if an attached tick tested "negative", other undetected ticks may have attached to a person and transmitted the bacteria. Additionally, the Rhode Island Department of Health stated that "The testing of ticks for the presence of the bacteria that causes Lyme disease has no role in the clinical diagnosis of Lyme disease".

Concurrent cat-scratch disease or Babesiosis is not, in and of itself, justification for long-term antibiotic therapy for LD. Babesiosis, an infection by a protozoan parasite which in some ways resembling malaria, is most often treated with intravenous or oral clindamycin for 7 days plus oral quinine, or oral atovaquone plus oral azithromycin (Gilbert\textsuperscript{16} et al, 2003).

Bartonellosis (infections with \textit{Bartonella} species) can create symptoms that mimic LD, and in some cases, co-infection can occur. \textit{Bartonella} can create granulomatous (cat-scratch disease), bacteremic (\textit{Bartonella} endocarditis, Oroya fever, and trench fever) or vasculoproliferative disease (bacillary angiomatosis-peliosis and verruga peruana). According to available guidelines, the diagnosis of both bacillary angiomatosis and cat-scratch disease rests on tissue examination (Warthin-Starry stains) and

\textsuperscript{14}Roos KL. AAN practice parameter: Antimicrobial therapy of neuroborreliosis. Journal Watch Neurology, October 2, 2007
serologic tests (immunosorbant or ELISA assay). *Bartonella* bacteremia is diagnosed with serologic tests and confirmed by blood culture. Oroya fever may be diagnosed by examining a peripheral blood smear. According to available guidelines, most patients with cat-scratch disease do not require more than symptomatic support. A fluctuant or suppurative lymph node may benefit from needle aspiration. Antibiotic therapy should be reserved for immunocompromised individuals or those with evidence of severe or systemic disease. Available guidelines state that severe cat-scratch disease is usually treated with oral doxycycline plus rifampin or ciprofloxacin. Antibiotic therapy for cat-scratch disease should be continued for at least 14 days. The treatment of choice for bacillary angiomatosis-peliosis is either oral erythromycin or oral doxycycline. Oral azithromycin is an alternative. Available guidelines state that patients who are severely ill or unable to absorb oral medications should be treated with intravenous formulations. Rifampin should be added to the regimen for patients in the former category. Because disease relapse is otherwise so common in these immunocompromised hosts, patients should be treated for at least 3 months. Verruga lesions do not respond consistently to antimicrobial agents and sometimes require surgical resection. *Bartonella* bacteremia also warrants antimicrobial treatment, despite the fact that some immunocompetent hosts with *B. quintana* bacteremia will clear their infection spontaneously. The same drugs for treatment of bacillary angiomatosis-peliosis are recommended for primary bacteremias. All patients should be evaluated for endocarditis.

According to available guidelines, oral therapy is usually sufficient for uncomplicated *Bartonella* bacteremia. Exceptions may include immunocompromised patients, bony or parenchymal involvement, and endocarditis, for which initial parenteral therapy may be advantageous. Treatment should be administered for at least 6 weeks and for 2 to 4 weeks in patients with and without endocarditis, respectively. Rifampin should be added to the regimen for treatment of endocarditis. Available guidelines state that patients with trench fever usually respond rapidly to oral antibiotic therapy with resolution of fever and other symptoms within 1 to 2 days. Relapses in treated patients have been well described. In patients with Oroya fever, available guidelines state that that penicillin, chloramphenicol, tetracycline, and streptomycin are effective. According to these guidelines, oral chloramphenicol for 7 or more days is the therapy of choice because of the frequent association of Salmonella infection in endemic regions. After the institution of therapy, fever generally disappears within 2 to 3 days, although blood smears may remain positive for some time.

Q fever is caused by Coxiella Brunetti (C.b.), an intracellular parasitic gram-negative bacterium. The most common hosts are goats, cattle, sheep, cats, and occasionally dogs. This spore-forming microorganism reaches high concentrations in the placenta of infected animals; with aerosolization occurring during parturition. Human Q fever usually results from inhalation of contaminated aerosol. There are 3 distinct clinical syndromes of the acute form of Q fever: (i) non-specific febrile illness, (ii) pneumonia, and (iii) hepatitis. The chronic form of the disease is usually endocarditis, but occasionally it is manifest as hepatitis, osteomyelitis or endovascular infection. The pneumonic form of the disease can range from very mild to severe pneumonia requiring assisted
Diagnosis of Q fever is based on isolation of the agent in cell culture, its direct detection, namely by PCR, and serology. Detection of high phase II antibodies titers 1 to 3 weeks after the onset of symptoms and identification of IgM antibodies are indicative to acute infection. High phase I IgG antibody titers of greater than or equal to 1:800 as revealed by micro-immunofluorescence offer evidence of chronic C.b. infection. For acute Q fever, a 2-week treatment with doxycycline is recommended as the first-line therapy. In the case of Q fever endocarditis a long-term combined antibiotic therapy (e.g., doxycycline plus quinolones, or doxycycline plus hydroxychloroquine) is necessary to prevent relapses (Marrie17, 2003). There is a lack of evidence regarding the use of intravenous antibiotic therapy for patients with Q fever. A recent review (Parker et al,18 2006) did not address the use of intravenous antibiotic therapy for the treatment of Q fever.

Ljostad et al (2007) examined the diagnostic sensitivity and temporal course of intra-thecal Borrelia burgdorferi (Bb) antibody production in acute Lyme neuroborreliosis (LNB) The authors concluded that the diagnostic sensitivity of Bb AI is suboptimal in acute early LNB. Repeated post-treatment Bb AI testing, to confirm or reject LNB diagnosis, is unreliable, as the majority of initial Bb AI negative patients remained negative at follow-up.

Blanc et al 19(2007) stated that the AI has a very good specificity but only moderate sensitivity in diagnosing LNB. These investigators noted that given the lack of consensual criteria for neuroborreliosis and the absence of a "gold standard" diagnostic test, they proposed pragmatic diagnostic criteria for neuroborreliosis, namely the presence of 4 of the following 5 items: (i) no past history of neuroborreliosis, (ii) positive CSF ELISA serology, (iii) positive anti-Borrelia AI, (iv) favorable outcome after specific antibiotic treatment, and (v) no differential diagnosis. They stated20 that these new criteria will need to be tested in a larger, prospective cohort.

Shoemaker et al21 (2008) stated that current laboratory markers do not readily detect acute LD. These researchers assessed the utility of complement and its split products as markers of LD in patients shortly after a tick bite. A total of 31 consecutive acute LD patients, 14 with and 17 without erythema migrans (EM) skin rash, seen by a physician within 96 hrs. of a tick bite were matched with 24 consecutive tick bite patients without LD symptoms and 46 healthy control subjects. Complement and split products measured included factor B, Bb, C4, C3c, C3a(des Arg), C4a(des Arg), C1q- and C3d-containing immune complexes, and C2. C2, C4, C3 and factor B levels were within normal ranges in all

18 Parker NR, Barralet JH, Bell AM. Q fever. Lancet. 2006;367(9511): 679-688
groups. C3a and C4a levels were significantly higher in acute LD patients than in tick bite and healthy control groups (both p < 0.001). All acute LD patients, regardless of EM, had elevated levels of C3a or C4a. Few tick bite controls had elevated levels of C3a (2/20) or C4a (5/24) and only 1 of the healthy control subjects had elevated C3a (0/46) or C4a (1/32). The authors concluded that these findings suggested that C3a and C4a may be useful markers of LD in patients seen shortly after tick bite, even in those without EM. They noted that the findings of this small study need to be confirmed in a larger study with clinical follow-up. Furthermore, additional studies are needed to evaluate the effects of B. garinii and B. afzelii (which are more common in Europe) infection on the complement system in patients with LD.

Single photon emission computed tomographic (SPECT) scans are often abnormal in patients with LD, but no pattern is specific for LD and these scans are often abnormal in patients without LD (Kalina et al(22, 2005). Halperin(23) (2010) stated that SPECT brain scans have been used with increasing frequency. In one study, quantitative SPECT, applied in a highly selected group of patients with well-characterized nervous system LD, showed patchy brain hypo-metabolism. However, qualitative brain SPECT, the technique used in clinical laboratories, is highly variable even in normal patients, and has no positive or negative predictive value in nervous system LD.

The European Federation of Neurological Societies' guidelines on the diagnosis and management of European Lyme neuroborreliosis (Mygland et al(24, 2010) stated that the following 3 criteria should be fulfilled for definite LNB, and 2 of them for possible LNB: (i) neurological symptoms; (ii) CSF pleocytosis; (iii) Bb-specific antibodies produced intra-thecally. Moreover, PCR and CSF culture may be corroborative if symptom duration is less than 6 weeks, when Bb antibodies may be absent. Otherwise, PCR is not recommended. Furthermore, there is insufficient evidence to recommend the following tests for diagnostic purposes: antigen detection, chemokine CXCL13, cyst formation, immune complexes, lymphocyte markers, lymphocyte transformation test, and microscope-based assays. Adult patients with definite or possible acute LNB (symptom duration less than 6 months) should be offered a single 14-day course of antibiotic treatment. Oral doxycycline (200 mg daily) and intravenous ceftriaxone (2 g daily) are equally effective in patients with symptoms confined to the peripheral nervous system, including meningitis. Patients with CNS manifestations should be treated with intravenous ceftriaxone (2 g daily) for 14 days and late LNB (symptom duration greater than 6 months) for 3 weeks. Children should be treated as adults, except that doxycycline is contraindicated under 8 years of age (9 in some countries). If symptoms persist for more than 6 months after standard treatment, the condition is often termed PLDS. Antibiotic therapy has no impact on PLDS.

Marques et al\textsuperscript{25} (2009) noted that it has been reported that patients with chronic LD have a decreased number of natural killer (NK) cells, as defined by the CD57 marker. These researchers performed immunophenotyping in 9 individuals with PLDS, 12 who recovered from LD, and 9 healthy volunteers. The number of NK cells was not significantly different between the groups. A review on Lyme borreliosis (Stanek \textsuperscript{26}et al, 2012) states that "measurement of the number of CD57 natural killer cells and use of live microscopy on blood to search for spirochetes, have not been shown to be reliable and are not recommended for clinical use". Also, an UpToDate review on "Diagnosis of Lyme disease" (Hu, 2012) does not mention measurement of NK cells as a diagnostic tool.

The practice guidelines by the Infectious Diseases Society of America on the "Clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and Babesiosis" (Wormser et al, 2006) did not mention the use of SPECT. Also, the AAN's practice parameter on "Diagnosis of Patients with Nervous System Lyme Borreliosis" (1996) includes no role for SPECT scans. A review article by Halperin\textsuperscript{27} (2008), who also was the first author of an AAN assessment on this issue, stated that “brain SPECT imaging is notoriously unreliable and is rarely helpful”.

An UpToDate review on "Nervous system Lyme disease" (Halperin, 2011) states that "[s]ince Lyme encephalomyelitis is so rare, MRI of the brain and spine is only rarely abnormal in Lyme disease. When present, encephalomyelitis is evident on MRI as areas of increased signal on T2 and FLAIR sequences. When these areas are large and active, positron emission tomography (PET) demonstrates them to be hypermetabolic. Single photon emission computed tomographic (SPECT) brain scans have been used with increasing frequency. In one study, quantitative SPECT, applied in a highly selected group of patients with well-characterized nervous system Lyme disease, demonstrated patchy brain hypometabolism. However qualitative brain SPECT, the technique used in clinical laboratories, is highly variable even in normal patients, and has no positive or negative predictive value in nervous system Lyme disease". Furthermore, an UpToDate review on "Diagnosis of Lyme disease" (Hu, 2012) does not mention the use of SPECT.

Schmidt et al\textsuperscript{28} (2011) examined chemokine CXCL13 as a potential biomarker for LNB. From March 2008 to August 2009, CSF and serum samples from all patients in whom a B burgdorferi-specific Al was requested (n = 692) and CSF analysis revealed CSF pleocytosis (n = 192) were included in the study. Because of the low number of patients with untreated LNB, 13 additional retrospectively selected samples of patients with untreated LNB were added The authors concluded that CXCL13 shows

\textsuperscript{25} Marques A, Brown MR, Fleisher TA. Natural killer cell counts are not different between patients with post-Lyme disease syndrome and controls. Clin Vaccine Immunol. 2009;16(8):1249-1250
high sensitivity and specificity for acute, untreated LNB. They stated that this novel marker has a high potential for use as a complimentary diagnostic tool for LNB. However, Tumani and Cadavid\textsuperscript{29} (2011) stated that there are several limitations to the current study. The editorialists noted that "[s]everal important issues remained to be answered with regard to the use of CSF levels of CXCL13 in patients with LNB .... Further studies are also needed to evaluate the usefulness of CSF levels of CXCL13 to determine the optimal duration of antibiotic treatment. This is of importance especially in cases with suspected "post-Lyme disease", which may represent a major challenge in routine clinical practice and may prompt physicians to use prolonged unjustified antibiotic treatment".

Klempner et al\textsuperscript{30} (2013) stated that the authors of 4 National Institutes of Health-sponsored antibiotic treatment trials of patients with persistent unexplained symptoms despite previous antibiotic treatment of Lyme disease determined that re-treatment provided little if any benefit and carries significant risk. Two groups recently provided an independent re-assessment of these trials and concluded that prolonged courses of antibiotics are likely to be helpful. These investigators have carefully considered the points raised by these groups, along with their own critical review of the treatment trials. On the basis of this analysis, the authors concluded that there is a meaningful clinical benefit to be gained from re-treatment of such patients with parenteral antibiotic therapy cannot be justified.

Lantos and colleagues\textsuperscript{31} (2014) stated that much of the controversy that surrounds Lyme disease pertains to whether it produces prolonged, treatment-refractory infection, usually referred to as chronic Lyme disease. Some have proposed that round morphologic variants of B. burgdorferi, known variably as "cyst forms" and "L-forms," are responsible for the pathogenesis of chronic Lyme disease. These investigators undertook a systematic review of the literature to determine if there is a documented role of these variants in Lyme disease pathogenesis or in syndromes compatible with chronic Lyme disease. The authors concluded that in the context of the broader medical literature, it is not currently possible to ascribe a pathogenic role to morphologic variants of B. burgdorferi in either typical manifestations of Lyme disease or in other chronic disease states that are often labeled chronic Lyme disease. They stated that there is no clinical literature to justify specific treatment of B. burgdorferi morphologic variants.

\textsuperscript{29} Tumani H, Cadavid D. Are high CSF levels of CXCL13 helpful for diagnosis of Lyme neuroborreliosis? Neurology. 2011;76(12):1034-1035
Newberg et al 32(2002) stated that there were no positron emission tomography (PET) studies reported in the literature with regards to brain metabolism and function in patients with Lyme disease. These patients frequently present with various neurological symptoms, including memory problems. These researchers used [(18)F]fluorodeoxyglucose (FDG) PET to determine the metabolic landscape in 23 patients with Lyme disease. The authors concluded that although there was no clear diagnostic pattern, and many of the defects were mild, FDG PET imaging may provide important information regarding the areas of the brain affected in patients with neurological symptoms associated with Lyme disease.

Kalina et al 33 (2005) noted that Lyme disease is a multi-system infectious disease caused by the tick-borne spirochete, B. burgdorferi. Central nervous system (CNS) involvement typically causes local inflammation, most commonly meningitis, but rarely parenchymal brain involvement. These investigators described a patient who presented with clinical findings suggesting a brainstem process. Magnetic resonance imaging (MRI) and PET suggested a brainstem neoplasm. Prior to biopsy, laboratory evaluation led to the diagnosis of Lyme disease. Clinical and imaging abnormalities improved markedly following anti-microbial therapy. The authors described Lyme disease involvement of the cerebellar peduncles with hyper-metabolism on PET. They stated that although MRI is the primary imaging modality for most suspected CNS pathology, the practical applications of PET continue to expand. However, an UpToDate review on “Diagnosis of Lyme disease” (Hu, 2013a) does not mention the use of PET as a management tool. Furthermore, the review does not mention testing for neuroadrenal expanded panel (including histamine, serotonin, and hydroxyindoleacetic acid (HIAA)).

An UpToDate review on “Treatment of Lyme disease” (Hu, 2013b) does not mention the use of intramuscular antibiotics of intravenous ascorbic acid as therapeutic options.

The iSpot Lyme assay measures cytokine production in-vitro, specifically interferon gamma, from T-cells in response to activation from Lyme antigen. The interferon-gamma ELISPOT (immunospot) has been used in Lyme disease research since the mid-1990s. A few scientific papers have investigated its use as a diagnostic test for Lyme disease; however, there is no consensus on its use.

Norberg et al 34(2012) examined the diagnostic performance of Borrelia (Bb)-induced interferon (IFN)-gamma secretion detected by ELISPOT modified to be feasible for clinical laboratories as a supplementary test to the laboratory diagnosis of Lyme neuroborreliosis (LNB) in an endemic setting. The authors concluded that the findings in this study showed that this ELISPOT-assay modified

to be feasible in clinical routine laboratories is not useful as a supplementary diagnostic tool in the laboratory diagnosis of patients with clinically suspected LNB.

Jin et al\(^\text{35}\) (2013) noted that Lyme Borreliosis is an infectious disease caused by the spirochete B. burgdorferi that is transmitted through the bite of infected ticks. Both B cell-mediated humoral immunity and T cell immunity develop during natural Borrelia infection. However, compared with humoral immunity, the T cell response to Borrelia infection has not been well-elucidated they demonstrated that the iSpot Lyme assay has a significantly higher specificity and sensitivity compared with the Western Blot assay that is currently used as a diagnostic measure. These preliminary findings need to be validated by well-designed studies. An UpToDate review on “Diagnosis of Lyme disease” (Hu, 2014) does not mention the use of iSpot/cytokine/interferon as a diagnostic tool/biomarker.

An UpToDate review on “Diagnosis of Lyme disease” (Hu, 2014) states that “Xenodiagnosis for Lyme disease involves the use of a tick vector to detect the presence B. burgdorferi. Although not clinically available, xenodiagnosis has been used to detect B. burgdorferi in animal and human studies. In one study, I. scapularis larvae were allowed to feed on 36 human participants (23 with a history of Lyme disease) until the larvae were engorged. The ticks were then tested for B. burgdorferi by polymerase chain reaction (PCR), culture, and/or isothermal amplification followed by PCR and electrospray ionization mass spectroscopy. Xenodiagnosis was well tolerated. Of the 23 patients with a history of Lyme disease, 19 tested negative for B. burgdorferi, two had indeterminate results and two tested positive by PCR, but not by culture. Of the two who tested positive, one had erythema migrans and was receiving antibiotics, and one had post–treatment Lyme disease. Further studies are needed to determine the sensitivity of xenodiagnosis in patients with Lyme disease, as well as the significance of a positive result”.

Puri et al\(^\text{37}\) (2015) noted that while pharmacotherapy with intravenous ceftriaxone, a third-generation cephalosporin, is a potential treatment of Lyme neuroborreliosis, there is concern that it can cause the formation of biliary sludge, leading to hepatobiliary complications such as biliary colic, jaundice and cholelithiasis, which are reflected in changes in serum levels of bilirubin and markers of cholestatic liver injury (alkaline phosphatase and gamma-glutamyltranspeptidase). It has been suggested that the naturally occurring substances alpha-lipoic acid and glutathione may be helpful in preventing hepatic disease. The authors concluded that co-administration of alpha-lipoic acid and

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\(^{36}\) Hu L. Diagnosis of Lyme disease. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed October 2014

\(^{37}\) Puri BK, Hakkarainen-Smith JS, Derham A, Monro JA. Co-administration of α-lipoic acid and glutathione is associated with no significant changes in serum bilirubin, alkaline phosphatase or γ-glutamyltranspeptidase levels during the treatment of neuroborreliosis with intravenous ceftriaxone. J Complement Integr Med. 2015;12(3):227-230
glutathione is associated with no significant changes in serum bilirubin, alkaline phosphatase or gamma-glutamyltranspeptidase levels during the treatment of neuroborreliosis with intravenous ceftriaxone.

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<th>CPT Codes / HCPCS Codes / ICD-10 Codes</th>
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<td><strong>Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by &quot;+&quot;:</strong></td>
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<td><strong>CPT codes covered if selection criteria are met:</strong></td>
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**HCPCS code covered if selection criteria are met:**
- S9494 - S9504 Home infusion therapy, antibiotic, antiviral, or antifungal therapy

**HCPCS code not covered for conditions listed in policy**
- G0219 PET imaging whole body; melanoma for non-covered indications
- G0277 Hyperbaric oxygen under pressure, full body chamber, per 30 minute interval
- G0235 PET imaging, any site, not otherwise specified
- G0252 PET imaging, full and partial-ring PET scanners only, for initial diagnosis of breast cancer and/or surgical planning for breast cancer (e.g. initial staging of axillary lymph nodes)
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<th>Code</th>
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<td>Injection, dimercaprol, per 100 mg</td>
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<td>Injection, edetate calcium disodium, up to 1000 mg</td>
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<td>Edetate disodium, per 150 mg</td>
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<td>IV chelation therapy (chemical endarterectomy)</td>
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<td>S9355</td>
<td>Home infusion therapy, chelation therapy; administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem</td>
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**ICD-10 code covered if selection criteria are met:**
- A69.20 Lyme disease, unspecified

**ICD-10 code not covered for indications listed in the CPB:**
- A28.1 Cat-scratch disease
- A44.0 - A44.9 Bartonellosis
- A78 Q fever
- B60.0 Babesiosis
- G51.0 Bell's palsy
- R53.82 Chronic fatigue, unspecified