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SPECIAL ARTICLE

Practice Parameter: Treatment of nervous system Lyme disease (an evidence-based review)

Report of the Quality Standards Subcommittee of the American Academy of Neurology

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ABSTRACT **Objective:** To provide evidence-based recommendations on the treatment of nervous system Lyme disease and post–Lyme syndrome. Three questions were addressed: 1) Which antimicrobial agents are effective? 2) Are different regimens preferred for different manifestations of nervous system Lyme disease? 3) What duration of therapy is needed? **Methods:** The authors analyzed published studies (1983–2003) using a structured review process to classify the evidence related to the questions posed. **Results:** The panel reviewed 353 abstracts which yielded 112 potentially relevant articles that were reviewed, from which 37 articles were identified that were included in the analysis. **Conclusions:** 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 neurologic symptomatology, or failure to respond to oral regimens. The number of children (≥8 years of age) enrolled in rigorous studies of oral vs 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 (Level A). **NEUROLOGY 2007;69:1–1**

STATEMENT OF PURPOSE The Quality Standards Subcommittee (QSS) develops scientifically sound, clinically relevant practice parameters to aid in the practice of neurology. This article addresses the use of antibiotic treatments in patients with nervous system Lyme disease and post-Lyme syndrome. These recommendations address the needs of medical providers caring for patients with these conditions.

Lyme disease is a multisystem infectious disease caused by the tick-borne spirochete *Borrelia burgdorferi*, which frequently affects the nervous system. Published guidelines are available to assist in the diagnosis of nervous system Lyme disease,[1] and for treatment of Lyme disease in general.[2] However, there continues to be considerable controversy and uncertainty about the best approach to treatment of neuroborreliosis. In the United States, Lyme disease affecting the nervous system is generally treated with parenteral antibiotics, although several European studies have demonstrated comparable efficacy with oral doxycycline, a drug that achieves adequate levels in the nervous system. Duration of treatment varies widely, with published recommendations ranging up to 4 weeks, despite a lack of compelling data supporting courses longer than 2 weeks. Some practitioners treat with combinations of antimicrobials for many months, despite an absence of data to indicate this is rational or effective. Finally, there is a lack of clarity as to which syndromes associated with Lyme disease reflect nervous system infection, which are consequences of infection outside the nervous system, and which are postinfectious.

The relevant literature was reviewed in detail to determine the following:

1. Which antimicrobial agents have been shown to be effective or ineffective in the treatment of nervous system Lyme disease

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2. If different regimens are preferred for different manifestations of neuroborreliosis

3. What duration of therapy is needed

DESCRIPTION OF THE ANALYTIC PROCESS In the spring of 2004 the Quality Standards Subcommittee (QSS) of the American Academy of Neurology (AAN) convened an expert panel of investigators from the United States and Europe who have published extensively in the field. The panel was selected to represent a broad range of relevant expertise and opinion.

In May 2004, a literature search was performed (all languages) using Ovid MEDLINE, Pubmed, and EMBASE, using search terms "Lyme Disease/[Drug Therapy, Therapy]," "Borrelia Infections/[Drug Therapy, Therapy]," "Borrelia burgdorferi group/ and (borreliosis or Borrelia or neuroborreliosis)," and "Anti-Infective Agents/[Therapeutic Use] and (antibiotic$ or antimicrob$ or anti-microb$)." This resulted in 353 citations. After elimination of duplicate citations, each abstract was reviewed by at least two members of the panel for relevance for further review. Any disagreements were arbitrated by a third reviewer. This resulted in a list of 112 articles, each of which was then reviewed by at least two members of the panel. Members of the panel recommended adding 10 additional references. After detailed review of all 122, the panel decided 37 articles contributed relevant, assessable data. Articles were excluded if they did not address treatment of neuroborreliosis, were not peer reviewed, or were solely review articles. The selected articles were then reviewed in detail by all panel members to assess the quality of the evidence contained.

Studies were divided into three groups: adult Lyme disease, pediatric Lyme disease, and post-Lyme syndrome. Each article was reviewed to determine if it specifically addressed treatment of neuroborreliosis, and if it contained original data. Those that were relevant were then graded as Class I through IV, using standard criteria, as listed in Appendix 2. An evidence table was constructed listing each study, its class, the treatment regimens assessed, whether it was prospective or retrospective, whether it was blinded or open, whether it was controlled or not, whether it used explicit or objective response criteria, the number of subjects, the duration of observation, the completeness of follow-up, and the outcomes.

Overall, four studies[5-7,47] were Class I (three in post-Lyme syndrome). One,[47] performed in children, was considered Class I with regard to its predetermined outcome measure, CSF antibiotic levels, but this study did not discuss clinical outcomes. Four studies were Class II (three in adults with neuroborreliosis,[15,18,19] one in children[48]). All were rated Class II with regard to at least one of their predetermined objective measures of disease activity: ELISA, CSF cell count or culture, all of which were apparently measured in masked fashion. All four of these studies would be considered Class III with regard to clinical outcomes, for which assessments were not masked. All other studies were Class III or IV.

ANALYSIS OF THE EVIDENCE When Lyme borreliosis affects the nervous system, it typically presents with (a) all or part of a triad—meningitis, cranial neuritis, and radiculoneuritis (known in Europe as Garin-Bujadoux-Bannwarth syndrome); (b) parenchymal inflammation of the brain or spinal cord; (c) mild radiculoneuropathy presenting as a more diffuse, predominantly sensory peripheral neuropathy[3,4]; or (d) encephalopathy (alteration of cognitive function of varying severity, with or without evidence of brain infection). Most well performed studies have focused on (a), the group in which the diagnosis is most clear-cut and treatment response is most straightforward to assess.

Parenchymal CNS involvement is quite rare, and studies of treatment of these individuals have largely been anecdotal (Class IV). Similarly, only a limited number of small studies have addressed (c) or (d); all are Class III or IV.

A separate entity, defined differently by different authors, often referred to as "post-Lyme syndrome," occurs in patients who have had Lyme disease, but, after treatment that would normally be expected to be effective, have continued to have residual chronic symptoms, including one or more of the following: musculoskeletal pain (without frank arthritis; fibromyalgia-like), fatigue, and "neuropsychiatric" symptoms. The latter typically consist of perceived memory or cognitive difficulty, irritability, sleep disturbance, depression, headache, limb or other paresthesias—all in the absence of clinical or laboratory evidence of focal or inflammatory central or peripheral nervous system involvement.[5-7] Thus, this entity is often included in discussions of neuroborreliosis, even though there is no evidence of CNS infection in such individuals. Although only three published studies have addressed this disorder, all have been Class I.

ADULT NEUROBORRELIOSIS Long before the characterization of Lyme disease, anecdotal reports[8,9] indicated that erythema migrans-associated meningitis was responsive to penicillin. The first treatment trial,[10] published in 1983, compared outcomes in 12 US patients with Lyme meningitis

treated with high dose IV penicillin to those in a group of patients evaluated previously and treated only with prednisone. Symptoms resolved far more quickly in penicillin-treated patients. No penicillin-treated patients had relapses following treatment, although several had residual symptoms. One eventually was retreated for persistent rheumatologic symptoms. The same year a Swedish study[11] reported 21 patients with chronic meningitis, subsequently shown to be due to *B burgdorferi*, who responded to IV penicillin. No control group was included; since these patients' illnesses had been unremitting prior to treatment, the authors considered the patients' pretreatment course as equivalent to an historical control. Although these studies were small and Class III, they indicated that neuroborreliosis was antibiotic responsive, just as other studies had shown that Lyme disease in general was antibiotic responsive.[12] Therefore no studies of treatment of neuroborreliosis have included placebo-treated patients.

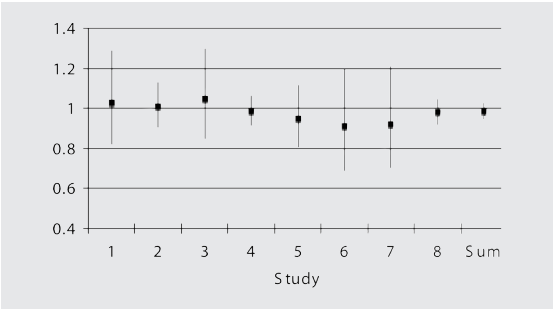
Subsequent studies have compared the efficacy of various regimens. In 1988, ceftriaxone and IV penicillin were first shown[13] to be comparably effective. Ceftriaxone doses of 2 g/day were shown to be as effective as 4 g/day (Class III). The same year, a consecutive series of 113 patients[14] with neuroborreliosis (Class IV), including 15 with encephalitis, treated with parenteral penicillin, doxycycline, or cefuroxime, was shown to have generally excellent responses (no comparisons among regimens). Subsequent studies compared parenteral doxycycline (200 mg/day for 2 days, then 100 mg/day for 8 days; n = 39) to parenteral penicillin (20 MU/day for 10 days, n = 36) (Class II with regard to CSF abnormalities; Class III clinical)[15]; cefotaxime (2 g, 3 times daily for 10 days) vs penicillin (5 MU 4×/day for 10 days) (Class III)[16]; cefotaxime (3 g, twice daily × 10 days; n = 69 of whom 49 had neuropathy) vs penicillin (20 MU/day × 10 days; n = 66, 44 with neuropathy) (Class III)[17]; and ceftriaxone (2 g/day × 10 days; n = 17) to cefotaxime (2 g every 8 hours x 10 days; n = 16) (Class II with regard to CSF abnormalities; Class III clinical).[18] In each study, both regimens demonstrated comparable rates of efficacy.[19-22]

Although most studies have focused on patients with Lyme meningoradiculitis, two have assessed treatment response in patients with Lyme encephalopathy, defined as objectively demonstrable cognitive abnormalities on formal mental status testing or neuropsychological testing. In the first[23] (Class III), 27 adults with Lyme encephalopathy, polyneuropathy, or both were treated with ceftriaxone, 2 g IV daily for 2 weeks. Response to therapy, as measured by clinical signs and symptoms, CSF analyses, and neuropsychologic testing, was gradual and typically was not apparent until several months following completion of treatment. Six months following treatment, 17 (63%) had improved, 6 (22%) improved but relapsed, and 4 (15%) were unchanged. Since symptoms had been prolonged and unremitting prior to treatment, this was believed to be due to the effect of treatment, even though no control group was included for direct comparison. A second study, in which CSF abnormalities were present in 89%, demonstrated efficacy of ceftriaxone (2 g daily for 30 days) in 18 adult patients with Lyme encephalopathy (Class III).[24] In this study, at 12 to 24 months follow-up, all patients were somewhat improved (2 patients; 11%), greatly improved (9 patients; 50%), or normal (7 patients; 39%).

While most studies demonstrated excellent responses to a wide range of antimicrobial regimens, several have raised the possibility that a significant number of patients may have residual difficulties. In one[25] (Class IV), 50 patients were identified who had intrathecal production of anti-*B burgdorferi* antibody. Of the 44 who were studied, 31 had cranial neuropathies, 12 radicular weakness, 12 other forms of weakness, 29 had pain, 11 had headache (multiple findings in most). At post-treatment follow-up, half the patients reported headache and concentration problems, although their neurologic deficits were better. The authors believed this represented an increase in subjective symptoms, despite improvement in objectively demonstrable abnormalities, similar to findings reported earlier.[26] However, in the earlier study fewer than 10% had residual cognitive complaints and the remaining individuals had symptoms suggestive of sequelae of disease, rather than ongoing infection. In another study[27] (Class IV) 25% of the patients assessed 5 years following treatment reported persistent "neurologic" difficulties. However, in this study, sequelae appeared to reflect neurologic damage at the time of infection, not ongoing infection or antibiotic treatment failure. Similarly, in a study of 36 patients[28] (Class IV) treated for Lyme meningitis, many described continued problems at 1 year follow-up. However, none appeared to develop new neurologic or arthritic signs or symptoms. Rather, symptoms ranged from nonspecific (headaches, myalgias) to residua of prior cranial or peripheral neuropathies.

Importantly, none of these follow-up studies included a control population. When this was done in a large case control study of patients (primarily with non-neurologic Lyme disease) in Connecticut,[29] patients who had been diagnosed with Lyme disease reported having increased difficulties and multiple

Figure Relative efficacy of doxycycline vs parenteral treatment



Relative efficacy of doxycycline vs parenteral treatment (ratio of response rate to doxycycline to response rate to parenteral penicillin or ceftriaxone; RR of 1.0 indicating identical response rates with the agents being compared) in eight studies, and in aggregate. Responses in most studies were judged clinically; in study 6, CSF criteria were used as well. For summed data, RR is 0.986 (95% CIs 0.948 to 1.025). Additional analyses of doxycycline vs parenteral penicillin or ceftriaxone individually and of parenteral penicillin vs ceftriaxone similarly showed no significant differences. Key to studies: #1[27]; #2[19]; #3[15]; #4[34]; #5[14]; #6[20]; #7[33]; #8[35].

symptoms, but in fact these symptoms occurred just as frequently in uninfected, age-matched controls.

Finally, two Finnish studies argued that longer courses of treatment might be necessary. One[30] (Class (III) described 60 patients treated for 100 days, half receiving 2 weeks of ceftriaxone followed by oral amoxicillin, the other half with oral cefixime for the entire period. Clear case definitions were not provided and the rationale for prolonged treatment was not clear; at 1 year follow-up 29/30 patients in each group were considered cured. No comparison group treated with conventional courses was included. A second study[31] described failure of conventional courses of ceftriaxone. Diagnostic criteria were not explicitly described in this article and a major criterion of treatment success was disappearance of symptoms, perhaps resulting in the conclusion that conventional treatment was ineffective based on premature assessment of symptom resolution.

Although numerous studies have demonstrated efficacy of parenteral antibiotic regimens in neuroborreliosis, there is also substantial evidence supporting the role of oral agents, particularly doxycycline. Pharmacologic studies[32] have demonstrated that in patients taking 200 mg of oral doxycycline daily, the CSF concentration exceeds the MIC for many but not all *B burgdorferi* strains. At least 10 studies have addressed the outcomes of treating neuroborreliosis with doxycycline.[12,14,15,19-22,27,33-35] All but two[14,34] used oral doxycycline; since blood levels achieved are comparable whether this drug is given orally or IV, data from these studies of IV doxycycline have been included. All studies were performed in Europe; most patients underwent CSF examination and were shown to have a CSF pleocytosis. No studies in US patients with neuroborreliosis have explicitly compared treatment response to oral doxycycline vs parenteral regimens. In the vast majority of studied patients, the clinical manifestation of neuroborreliosis was meningitis, facial nerve palsy, or radiculitis. A very few patients had evidence of parenchymal spinal cord or brain involvement. None of the studies was blinded; not all were randomized or prospective. To compensate for this lack of blinding, many used sequential lumbar punctures, using a decline in CSF mononuclear pleocytosis as an objective marker of treatment success. In one study,[19] in which outcome was judged by CSF improvement as well as clinical criteria, doxycycline (200 mg orally daily for 14 days; n = 31) was shown to be comparable to IV penicillin (3 g every 6 hours for 14 days; n = 23) in patients with Lyme meningitis with or without other associated nervous system involvement (Class II). A nonrandomized comparison of patients with meningitis demonstrated comparable CSF and clinical responses to ceftriaxone (2 g/day, 10 to 14 days, n = 29, and oral doxycycline 400 mg/day, 10 to 14 days, n = 36) (Class III).[20]

Other studies, without comparison groups, have shown high rates of efficacy with doxycycline (200 to 400 mg/day, 9 to 17 days, 34 patients with meningitis, facial palsy; no comparison group) (Class III)[21]; doxycycline (200 mg/day in most, one with 100 mg/day, one with two initial days of 400 mg, treatment duration 10 to 28 days; 6 with encephalomyelitis, 63 with meningitis/cranial neuritis/radiculitis) (Class IV)[22]; and doxycycline (200 to 400 mg/day × 10 to 19 days; 37 patients with meningitis with or without other abnormalities, including 7 with myelopathy, in a manuscript submitted for publication, but not yet accepted) (Class III).[36]

Altogether, these studies provide data on 300 patients with definite neuroborreliosis, treated with doxycycline. In no study were outcomes demonstrably different whether patients received doxycycline or parenteral beta-lactam regimens. Fifteen doxycycline-treated patients were retreated for persistent symptoms; none developed late neurologic sequelae, even though follow-up for some was as long as several years. Aggregating the data from the eight studies that compared doxycycline to parenteral regimens (figure), the overall response rate to doxycycline was 98.6% of the response rate to parenteral penicillin or ceftriaxone (95% CIs 94.8% to 102.5%). Given the very narrow CI, it is highly unlikely that there is a clinically or statistically significant difference between these regimens.

Although only two of these studies were Class II and none Class I, they do appear to demonstrate the low probability of developing late neurologic sequelae following treatment with oral doxycycline. Similarly, at least one US study[37] demonstrated no long-term adverse health outcomes in children treated for Lyme disease associated facial palsy (84% treated with oral doxycycline or amoxicillin,

16% with ceftriaxone). Interpretation of such negative findings in relatively small studies must be tempered, though, with an appreciation of the generally benign long-term outcome in many patients with acute neuroborreliosis. A 1990 German study[34] compared outcomes in 66 antibiotic-treated patients with neuroborreliosis to outcomes in 57 patients evaluated before the identification of the infectious cause of this syndrome and therefore never treated. The majority of patients in both groups (59% of untreated, 62% treated) were asymptomatic at long-term follow up; no patients in either group had evidence of recurrent or progressive disease.

Although it is likely that US patients with the same manifestations of neuroborreliosis will similarly be doxycycline responsive, there are differences between the *B burgdorferi* strains and species prevalent in the United States and Europe; hence the data may not be fully applicable. However, European studies[38,39] assessing the susceptibility of different *Borrelia* strains to multiple antimicrobials, including doxycycline, have found no significant differences in minimal inhibitory concentrations among the different species. Minimal bactericidal concentrations (MBCs) have been more variable[39] but for doxycycline were comparable for all species. In light of these observations, treatment responses might be expected to be comparable in US and European patients; however, this remains untested.

In the United States in particular, there has been a general reluctance to treat CNS *B burgdorferi* infections with oral regimens. Since several studies have shown[40,41] that many patients with nervous system Lyme disease have a vigorous CSF pleocytosis without symptoms of meningitis, some recommend routinely examining CSF in patients with suspected neuroborreliosis (e.g., Lyme disease associated facial nerve palsy), and treating those with a pleocytosis with parenteral regimens. Since no Class I studies, with good long-term follow-up, prove that oral treatment of Lyme meningitis is as effective as parenteral therapy with beta-lactam agents, particularly in patients infected with US strains of *B burgdorferi*, treatment with parenteral beta lactam agents is reasonable. However, given the absence of evidence of late CNS complications following oral antibiotic treatment of Lyme meningitis in all trials performed to date, coupled with the potential for greater morbidity associated with parenteral regimens, initial treatment with oral doxycycline, without a lumbar puncture, also appears to be a safe and valid approach to treatment—at least of facial nerve palsy.[42]

Notably, the only oral regimen that has been shown to be effective in neuroborreliosis is doxycycline—a drug with good CNS penetration. Amoxicillin and cefuroxime axetil, which are useful in non-neurologic Lyme disease, may be useful in neuroborreliosis patients who cannot take doxycycline, but data in support of this are purely inferential—namely, the absence of observed long-term sequelae in individuals treated with these medications,[37] an observation subject to the previously noted limitations.

The role of corticosteroids in patients with neuroborreliosis remains unclear. No prospective trials have addressed this question. The issue arises most frequently in patients with facial nerve palsy, since some guidelines for treatment of idiopathic facial nerve palsy[43] but not others[44] recommend their routine use. Early anecdotal observations suggested that patients with Lyme arthritis who received steroids were more difficult to cure[13,45]; however, steroids may well have been used in these patients because they already had more severe disease. In some animal models, nervous system disease is more pronounced if corticosteroids are administered.[46] In contrast, anecdotal studies have suggested outcomes in patients with severe radicular pain[47] or encephalomyelitis[48] may be improved if corticosteroids and antibiotics are administered concurrently. One large retrospective review[49] of 101 patients with Lyme disease-associated facial nerve palsy found no significant difference in outcome regardless of treatment (antibiotics in 37, steroids alone or in combination with antibiotics in 44, no treatment in the remainder), although the only patient in the group with severe residua had received steroids. In a 10- to 20-year follow-up study of patients with Lyme disease,[50] including 31 patients with facial nerve palsy, there was no difference in long-term outcome between those who had received steroids and those who had not. In sum, the limited available data suggest no clear beneficial or harmful effect of steroids in patients with neuroborreliosis who are treated with appropriate antimicrobial therapy.

PEDIATRIC NEUROBORRELIOSIS A wide range of Lyme disease-associated neurologic disorders has been described in children, including cranial neuropathies, headache, seizures, meningitis, meningoencephalitis, encephalopathy, focal neurologic signs, ataxia, vertigo, chorea, and transverse myelitis. Information comes from case reports, small series of patients, and from studies mainly focused on rheumatologic aspects of the disease, conducted shortly after Lyme disease was recognized as a distinct clinical entity.[51-53] More recent studies in both Europe and the United States addressing neurologic

involvement in cohorts of larger size show facial nerve palsy and meningitis to be the most frequent neurologic syndromes in children.[41,51,54] In contrast to adult Lyme disease patients, Bannwarth's syndrome (meningoradiculitis) and mild radiculoneuritis are uncommon and encephalopathy rare.[51]

As in adults, there are relatively few studies specifically assessing efficacy of treatment of neuroborreliosis in children. Only one study identified in the literature review was rated as Class I (but did not address clinical treatment response). In this study, 75 children with Lyme neuroborreliosis were randomized to receive IV treatment with either penicillin G or ceftriaxone.[55] On the 10th day of treatment, paired samples of serum and CSF were tested to determine the antibiotic concentration in each sample. CSF concentrations of both drugs exceeded the minimal inhibitory concentration, though, not surprisingly, the duration for which this was true was substantially greater for ceftriaxone (>24 hours) than for penicillin. The authors concluded that both drugs likely would be effective for treating Lyme neuroborreliosis, but no specific treatment response data were provided. In the only Class II study,[56] 23 children with Lyme neuroborreliosis were randomized to receive 14 days of IV treatment with either penicillin G or ceftriaxone. All children did well and none had sequelae at follow-up ≥6 months later. The investigators concluded that treatment with either drug was highly effective.

All of the remaining studies were categorized as either Class III or Class IV. Most were case series although there was one cross-sectional survey with controls, an observational study of 169 children with Lyme neuroborreliosis[54] (facial nerve palsy: 55%; meningitis: 27.2%; Bannwarth's syndrome: 3.6%; meningoencephalitis: 3.6%; "Guillain-Barré": 1.8%) in Lower Saxony in Germany. Although the focus of the study was on the epidemiology and the diagnosis of neuroborreliosis, virtually all of the children were treated IV with penicillin for 10 to 14 days and all had excellent outcomes. In a Swedish study, 203 children with Lyme neuroborreliosis were treated IV with penicillin (53 children), ceftriaxone (109 children), or cefotaxime (19 children) or orally with doxycycline (22 children).[35] At follow-up, symptoms and signs resolved in 58% of the children by the end of treatment, in 92% by 2 months and in all children by 6 months after treatment (three were lost to follow-up). In a retrospective Austrian study of 160 children with Lyme disease (45 [28%] with meningitis, facial palsy, or both[33]), 33 received ceftriaxone IV, 7 received benzylpenicillin IM, and 5 received doxycycline orally. All were treated for 10 to 21 days. All 151 children seen at 3-month follow-up recovered completely. In a series of 187 Danish patients with Lyme neuroborreliosis, 40 (21%) were children.[40] Most received penicillin G IV and all apparently did well at follow-up months to years later. In a US study, children with Lyme neuroborreliosis[57] (facial nerve palsy n = 6; meningitis n = 4, overlap not specified) were identified prospectively from a cohort of 201 children with Lyme disease. The children were treated with a variety of antibiotic regimens. Ceftriaxone IV was administered to three children with meningitis, two with facial nerve palsy, and one with facial nerve palsy and meningitis. The other children received orally administered antibiotics (amoxicillin, doxycycline, erythromycin, or penicillin). At follow-up none reported sequelae.

Nine Swedish children with Lyme neuroborreliosis were treated with penicillin G IV.[58] All but one (a child whose facial palsy persisted for 3 months) had prompt improvement and cure of their illnesses. At follow-up 3 months later all were asymptomatic and appeared to be cured. Although one report of follow-up of 63 children with erythema migrans was identified by our search,[53] only one of the children had neuroborreliosis (facial nerve palsy). In any case, all of the children in the report were well at follow-up. Finally, 43 children with facial nerve palsy due to Lyme disease were assessed 7 to 161 months (mean: 49 months) after infection.[37] Of these, 84% had been treated orally with either doxycycline or amoxicillin; the remainder had received ceftriaxone. Twenty of the patients underwent neuropsychological testing and all had average or above average scores on a large battery of tests. Although children with facial nerve palsy were more likely than normal matched controls to report musculoskeletal pain, changes in behavior, and numbness, reports of problems with activities of daily living were similar among affected patients and matched controls. The investigators concluded that the long-term neuropsychological and health outcomes of children with facial nerve palsy due to Lyme disease were comparable to those who did not have Lyme disease.

Conclusions. Based on four Class II studies antibiotic regimens have been established as probably safe and effective for both children and adults. One Class I and one Class II study suggest that parenteral regimens are probably safe and effective for severe neurologic disease but two Class II studies[15,19] and numerous Class III and IV studies suggest that oral treatment, particularly with doxycycline, is comparably safe and effective in many situations not involving parenchymal CNS involvement. Although the evidence is stronger in adults than chil-

Table 1 Antimicrobial regimens used in treatment of nervous system Lyme disease

Medication	Adult dose	Pediatric dose	Classification
Oral regimens			
Doxycycline* (preferred)	100 (–200) mg BID	≥8 yo: 4 (–8) mg/kg/d in 2 divided doses; max 200 mg/dose	B
Amoxicillin (when doxycycline contraindicated)†	500 mg TID	50 mg/kg/d in 3 divided doses; max 500 mg/dose	C
Cefuroxime axetil (when doxycycline contraindicated)†	500 mg BID	30 mg/kg/d in 2 divided doses; max 500 mg/dose	C
Parenteral regimens			
Ceftriaxone	2 g IV daily	50–75 mg/kg/d in 1 dose, max 2 g	B
Cefotaxime	2 g IV Q8H	150–200 mg/kg/day in 3–4 divided doses; max 6 g/day	B
Penicillin G‡	18–24 MU/d, divided doses Q4H	200–400,000 U/Kg/d divided Q4H, max 18–24 MU/day	B

For all, recommended duration is 14 days, although published studies have used courses ranging from 10 to 28 days, without significantly different outcomes.
*Tetracyclines are relatively contraindicated in children <8 years of age or in pregnant or lactating women.
†These two oral regimens are effective in non-nervous system Lyme borreliosis. There are no data demonstrating efficacy in neuroborreliosis but large numbers of patients have been treated with these regimens for other forms of Lyme disease without obvious subsequent onset of nervous system involvement. As such they may be an oral alternative in individuals who cannot take doxycycline.
‡The antibiotic dosage should be reduced for patients with impaired renal function.

dren, all available evidence indicates that the responses to oral treatment are comparable in adults and children. However, it must be emphasized that no definitive data exist to establish the superiority—or lack thereof—of either oral or parenteral treatment. Specific regimens are listed in tables 1 and 2.

POST-LYME DISEASE **Post-Lyme syndrome.** As discussed above, patients who have received accepted antibiotic regimens for various forms of Lyme disease sometimes have residual chronic symptoms, referred to variably as post-Lyme syndrome (PLS), post-Lyme disease syndrome, post-treatment chronic Lyme disease (PTCLD), or even chronic Lyme disease. There has been controversy as to whether PLS is a form of active infection in which the organism is difficult or impossible to eradicate from various "privileged" sites vs a postinfectious or noninfectious type of chronic fatigue syndrome, in which there is no ongoing infection. Arguments offered to support the possibility of persistent active infection derive from the apparent similarity between these symptoms and patients' perceptions of the cognitive difficulty and fatigue noted with untreated or partially treated Lyme disease; however, in patients with untreated or incompletely treated Lyme disease, these symptoms are typically associated with objective abnormalities on physical or laboratory examination, and symptoms and abnormal findings clearly respond, frequently with symptom resolution, to a 2- to 4-week course of IV antibiotics.[24,59]

Most available data argue against persistent *B burgdorferi* infection in patients who have received what are normally curative courses of antimicrobial therapy. First, antibiotic resistance has not been demonstrated in this genus.[60-62] Second, persistent symptoms do not correlate with any objective measure of nervous system disease or with laboratory measures of inflammation.[5,63] Third, there is no precedent for such a phenomenon in other spirochetal infections.[64] Fourth, anti-*B burgdorferi* antibody concentrations often decline, even to undetectable levels, despite persistent symptoms.[5,63,65] Such a decline in antibody in the face of persistent infection appears to be without precedent in other bacterial infections. Fifth, Lyme disease lacks characteristics of other infections that justify longer treatment courses, such as infections in which available antimicrobials have poor in vitro activity against the organism, infections caused by an intracellular pathogen, or infections involving a biofilm. Finally, patients with PLS do not respond to a further course of IV antibiotics. Anecdotally, some experience a subjective improvement while on antibiotics, with symptoms recurring rapidly following medication discontinuation, suggesting a placebo effect. Still, based on a transient improvement in symptoms, some physicians have treated patients with PLS with various antibiotic regimens for months to years.

Table 2 Syndromes and treatment options

Syndrome	Treatment options
Meningitis	Parenteral, particularly if severe*
	Doxycycline PO†
Any neurologic syndrome with CSF pleocytosis	Parenteral, particularly if severe*
	Doxycycline PO†
Peripheral nerve (radiculopathy, diffuse neuropathy, mononeuropathy multiplex, cranial neuropathy; normal CSF)	Doxycycline PO†
	Parenteral if treatment failure or if severe
Encephalomyelitis	Parenteral
Encephalopathy	Parenteral
Post-treatment Lyme syndrome	No antibiotics indicated; symptomatic management only

*Available data in European neuroborreliosis indicate that oral doxycycline and parenteral ceftriaxone are equally effective in Lyme meningitis, and anecdotal data from the United States indicate that in patients with Lyme disease–associated facial palsy, response to oral treatment is sufficient that CSF examination may be unnecessary. Although none of these studies is Class I, it was the consensus of the panel that, in the absence of brain or spinal cord involvement, oral treatment of neuroborreliosis is an acceptable option in appropriate circumstances.
†Studies assessing oral treatment of neuroborreliosis have only used doxycycline. Other agents such as amoxicillin or cefuroxime axetil may be effective in individuals who cannot tolerate doxycycline but relevant data are lacking.

To address this controversy, three randomized, double-blind placebo-controlled trials of antibiotic therapy in PLS have been published in adults with well-documented Lyme disease who had previously received accepted initial courses of antibiotics for acute disease but who had residual symptoms typical of PLS.

The first pair of trials, with a combined total of 129 patients, was reported initially in a single article, in which patients were divided into two groups: one seropositive, one seronegative. Treatment response, reported in each group as a separate trial, was measured using the physical and mental health-related quality of life components of the Medical Outcomes Study 36-item short form general health survey (SF-36) as the primary outcome measure.[5] A second article[7] assessed whether neurocognitive changes occurred in the same population, measuring attention, memory, and executive functioning using a battery of neuropsychological tests as one set of primary outcome measures. Mood and other psychiatric symptoms were assessed using the Beck Depression Inventory (BDI) and the Minnesota Multiphasic Personality Inventory (MMPI-2) as an additional set of primary outcome measures. Entrance criteria were symptoms of classic Lyme disease, physician-documented recommended treatment of Lyme disease, and typical musculoskeletal or cognitive PLS symptoms often accompanied by fatigue that had begun within 6 months of the initial infection, and that had been present for at least 6 months (but less than 12 years). Patients could be either seropositive or seronegative, but were excluded if they had previously received IV antibiotics for 60 or more days, had known hypersensitivity to study medications, had active synovitis or positive PCR for *B burgdorferi* gene segments in CSF or blood. Patients were evaluated at baseline, were randomized to receive either placebo or IV ceftriaxone 2 g/day for 30 days followed by oral doxycycline 200 mg/day for 60 days, and then re-evaluated at 1, 3, and 6 months.

For the combined group of 129 patients, at baseline the physical component of the SF-36 score was about 1.5 SD below and the mental component about 0.5 SD below that of age-matched norms, indicating significant impairment in health-related quality of life.[5] By contrast, although the baseline BDI showed mild to moderate depression, there was no significant difference in neuropsychological test measurements in the combined patient group vs age-matched norms.[7] There was also no significant difference in baseline SF-36, BDI, or neuropsychological test measurements in seropositive vs seronegative patients.

At 6 months, there was no significant difference in the SF-36,[5] neuropsychological test, and BDI measurements[7] between patients who had received placebo vs antibiotic therapy. Notably, about 40% of patients in each group (i.e., placebo and antibiotic) improved in the total SF-36 summary score at 6 months, while about 30% were unchanged and 30% were worse. Similarly, several neuropsychological test and BDI measurements improved at 6 months in both placebo- and antibiotic-treated patients.

The other trial[6] investigated potential changes in fatigue, cognitive function, and CSF clearance of *B burgdorferi* antigen in 55 patients with PLS. The primary outcome measures were (a) improvement in fatigue on a global fatigue severity measure (FSS-11); (b) improvement in mental speed on the A-A test, a computerized reaction time task of cognitive processing speed; and (c) CSF clearance of *B burgdorferi* OspA antigen. Entrance criteria were physician-documented erythema migrans, or a CDC-defined late manifestation of Lyme disease confirmed by positive ELISA and Western blot, completion of a recommended course of antibiotic

treatment, and severe persistent fatigue (typically accompanied by other musculoskeletal or neuropsychiatric symptoms of PLS) coincident with initial infection. Patients were excluded if they had known cephalosporin hypersensitivity or a confounding medical or severe psychiatric disorder. Patients were evaluated at baseline, were randomized to receive either placebo or IV ceftriaxone 2 g/day for 28 days, and then re-evaluated at 1 and 6 months.

At 1 month, fatigue improved in both antibiotic- and placebo-treated groups. At 6 months, there was a significant improvement in the FSS-11 fatigue score in patients treated with ceftriaxone compared to placebo, with no improvement in mental speed (or any of the other secondary neuropsychological tests) or in clearance of CSF antigen (although antigen was detected in CSF of only 16% of the patients at baseline) in the antibiotic vs placebo group. Subgroup analysis showed that improvement in the fatigue score after ceftriaxone particularly occurred in patients who had received an initial oral rather than IV course of antibiotics for acute Lyme disease. Of note, patients in the ceftriaxone group more often guessed that they were on active treatment than did the placebo patients, suggesting that blinding of patients may have been compromised and that improvement in fatigue in the ceftriaxone group may have been due to placebo effect. Importantly, the authors point out that the adverse events associated with parenteral antibiotic therapy do not justify such therapy for fatigue, a problem which might respond to safer symptomatic management.

An additional controlled treatment trial[66] presented to date only in abstract form evaluated 10 weeks of ceftriaxone treatment vs placebo in a total of 37 patients. Preliminary findings appear to indicate lack of sustained improvement in cognitive function in the antibiotic-treated patients at 14 weeks post-treatment follow-up. Although this is a much anticipated, NIH-funded trial, since it has not yet been published, its methodology, detailed conclusions and validity cannot be assessed, and it has not been included in the analysis.

In summary, published antibiotic treatment trials of PLS provide compelling Class I evidence that PLS is not due to active *Borrelia* infection and is not responsive to further antibiotic therapy, particularly with respect to overall health-related quality of life and cognitive and depressive symptoms. Whether profound fatigue in PLS is antibiotic responsive is still an open question but the data on this point are partially confounded and, as noted above, the authors of the study of fatigue in PLS do not endorse further antibiotic therapy for this symptom. The available studies confirm the importance of placebo effect that obscures interpretation of symptom improvement in individual patients with PLS treated with antibiotics.

Finally, in PLS there is dissociation between perceived problems with cognition and memory (which are often also present in association with depressive symptoms) and normal neuropsychological testing.[7] In contrast to individuals with PLS, patients with prior untreated or partially treated Lyme disease with late cognitive symptoms (which typically are milder than in PLS) often have abnormalities on neuropsychological testing, CSF, or imaging studies. The latter patients may well have active infection (e.g., Lyme encephalopathy), and often respond to IV ceftriaxone with resolution of symptoms.

Conclusions. Several Class I studies indicate that the disorder referred to as post-Lyme syndrome does not respond to prolonged courses of antibiotics and that such treatment can be associated with serious adverse events (see below).

RECOMMENDATIONS

1) Parenteral penicillin, ceftriaxone, and cefotaxime are probably safe and effective treatments for peripheral nervous system Lyme disease and for CNS Lyme disease with or without parenchymal involvement (Level B recommendation).
2) Oral doxycycline is probably a safe and effective treatment for peripheral nervous system Lyme disease and for CNS Lyme disease without parenchymal involvement (Level B recommendation). Amoxicillin and cefuroxime axetil may provide alternatives but supporting data are lacking.
3) Prolonged courses of antibiotics do not improve the outcome of post-Lyme syndrome, are potentially associated with adverse events, and are therefore not recommended (Level A recommendation).

COMMENT ON TREATMENT SAFETY Although the antimicrobial regimens discussed are widely used and generally well tolerated, none is without potential side effects. In one of the studies of post-Lyme syndrome,[6] 12 of the 28 patients receiving ceftriaxone developed diarrhea, while 4 developed allergic reactions (1 anaphylaxis, 3 minor). Because of its biliary excretion, ceftriaxone tends to cause pseudolithiasis (precipitation of the drug in the gall bladder), and may be associated with pseudomembranous colitis more frequently than other antimicrobials. Of the 55 patients (treated and placebo) who had indwelling IV access catheters, 3 developed

line sepsis (1 of 28 on ceftriaxone). One other treated patient in this study developed anaphylaxis while 10 developed less severe adverse events. In the other published pair of long-term treatment trials,[5] 27 of 129 patients developed adverse effects (16 of 64 receiving ceftriaxone), 2 of which (both patients on ceftriaxone) were life threatening (1 pulmonary embolism, 1 fever and GI bleed). Combining treated patients in these three studies, life-threatening complications occurred in 1 per 23, while overall, adverse events occurred in about 1 of every 3 treated patients.

Although oral doxycycline avoids issues related to line infections, the drug is associated with gastric irritation and with photosensitization. The latter is particularly problematic since most acute manifestations of Lyme disease occur in summer and autumn. Tetracyclines also cause abnormalities of developing bones and teeth in the fetus and in children under age 8.

RECOMMENDATIONS FOR FUTURE RESEARCH

Questions remain regarding the preferred therapeutic approach in early neuroborreliosis, particularly among US patients. The efficacy of oral doxycycline compared to a parenteral regimen such as ceftriaxone needs to be clearly established, as does the predictive value of CSF abnormalities. Assuming oral doxycycline is shown to be effective, it would then be helpful to assess the relative efficacy of other oral regimens such as amoxicillin or cefuroxime axetil.

Similarly, the optimal approach to the very rare entity of parenchymal CNS neuroborreliosis remains undefined. An assessment of preferred treatment duration, as well as a clear determination of the correct metrics of successful treatment, would be very helpful.

Although it is clear that prolonged antimicrobial therapy is not helpful in the treatment of post-Lyme syndrome, this entity will remain problematic until its pathophysiology is better understood.

MISSION STATEMENT OF QSS

The mission of the QSS is to prioritize, develop, and publish evidence-based practice parameters related to the diagnosis, treatment, and prognosis of neurologic disorders. The QSS is committed to using the most rigorous methods available within our budget, in collaboration with other available AAN resources, to most efficiently accomplish this mission.

DISCLAIMER

This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved.

CONFLICT OF INTEREST STATEMENT

The American Academy of Neurology is committed to producing independent, critical and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guidelines have been reviewed by at least three AAN committees, a network of neurologists, *Neurology* peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com.

APPENDIX 1

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APPENDIX 2

AAN classification of evidence for therapeutic intervention

Class I: Prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population. The following are required:

(a) primary outcome(s) clearly defined

(b) exclusion/inclusion criteria clearly defined

(c) adequate accounting for drop-outs and cross-overs with numbers sufficiently low to have minimal potential for bias

(d) Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences

Class II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets a–d above OR a RCT in a representative population that lacks one criterion a–d.

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.*

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion.

*Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data)

APPENDIX 3

Classification of recommendations

A = Established as effective, ineffective, or harmful for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)

B = Probably effective, ineffective, or harmful for the given condition in the specified population. (Level B rating requires at least one Class I study or at least two consistent Class II studies.)

C = Possibly effective, ineffective, or harmful for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U = Data inadequate or conflicting; given current knowledge, treatment is unproven.

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