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EFNS GUIDELINES/CME ARTICLE

EFNS guidelines on the diagnosis and management of European Lyme neuroborreliosis

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Background: Lyme neuroborreliosis (LNB) is a nervous system infection caused by *Borrelia burgdorferi sensu lato* (*Bb*).
Objectives: To present evidence-based recommendations for diagnosis and treatment.
Methods: Data were analysed according to levels of evidence as suggested by EFNS.
Recommendations: The following three criteria should be fulfilled for definite LNB, and two of them for possible LNB: (i) neurological symptoms; (ii) cerebrospinal fluid (CSF) pleocytosis; (iii) *Bb*-specific antibodies produced intrathecally. PCR and CSF culture may be corroborative if symptom duration is <6 weeks, when *Bb* antibodies may be absent. PCR is otherwise not recommended. There is also not enough evidence to recommend the following tests for diagnostic purposes: microscope-based assays, chemokine CXCL13, antigen detection, immune complexes, lymphocyte transformation test, cyst formation, lymphocyte markers. Adult patients with definite or possible acute LNB (symptom duration <6 months) should be offered a single 14-day course of antibiotic treatment. Oral doxycycline (200 mg daily) and intravenous (IV) ceftriaxone (2 g daily) are equally effective in patients with symptoms confined to the peripheral nervous system, including meningitis (level A). Patients with CNS manifestations should be treated with IV ceftriaxone (2 g daily) for 14 days and late LNB (symptom duration >6 months) for 3 weeks (good practice points). Children should be treated as adults, except that doxycycline is contraindicated under 8 years of age (nine in some countries). If symptoms persist for more than 6 months after standard treatment, the condition is often termed post-Lyme disease syndrome (PLDS). Antibiotic therapy has no impact on PLDS (level A).

Introduction

Lyme neuroborreliosis (LNB) is an infectious disorder of the nervous system caused by tick-borne spirochetes of the *Borrelia burgdorferi* (*Bb*) *sensu lato* complex. Clinical features of LNB are diverse and differ in European and American patients – most probably because of different bacteria species.

Laboratory confirmation of LNB is hampered by the low yield of culture and of polymerase chain reaction (PCR) examination of CSF [1,2]. Presence of *Bb*-specific antibodies in the CSF with evidence of intrathecal production is the traditional diagnostic gold standard, but has limitations such as low sensitivity in the very early phase of the disease [3–5] and persistence for years after eradication of the infection [6,7]. Several other, more or less validated, laboratory tests have been developed to improve diagnosis.

Lyme neuroborreliosis should be treated with antibiotics to achieve rapid resolution of symptoms and theoretically to avoid spreading and persistence of infection. The choice of the best antibiotic, the preferred mode of administration, and the duration of treatment are the still debated issues.

The purpose of this guideline is to present evidence-based recommendations for diagnostic evaluation and management of European LNB.

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The analytic process

Data were collected by searching MEDLINE, EMBASE, the Cochrane databases and other evidence-based guidelines and reviews, including the practice parameters proposed by the American Academy of Neurology [8] and The Infectious Diseases Society of America guidelines [9]. The search terms Lyme disease and LNB were cross-referenced with encephalopathy, meningitis, peripheral nervous system (PNS) disease, peripheral facial palsy, laboratory test, diagnosis and treatment. For determining levels of evidence, the EFNS guidelines were used [10]. Review articles and book chapters were also included if they were considered to provide comprehensive reviews of the topic. The final choice of literature and the references included were based on our judgement of their relevance to this subject. Two authors independently assessed quality of treatment trials. Recommendations were reached by consensus of all Task Force participants by a modified Delphi method and were also based on our own awareness and clinical experience. Where there was lack of evidence but consensus was clear, we have stated our opinion as good practice points (GPP).

Diagnostic evaluation

Clinical features of LNB

Neurological symptoms usually occur 1–12 (mostly 4–6) weeks after the tick bite, and mainly from July to December. Only 40–50% of the patients can recall a tick bite, and 20–30% report a local skin infection (erythema migrans) (stage I) [11,12]. More than 95% can be classified as early LNB (stage II), defined as signs and symptoms lasting for <6 months. Less than 5% have late LNB (stage III) with duration between 6 months and several years [12]. The natural course of early LNB is often self-limiting [13], whereas late LNB has a chronic course that probably reflects persistent survival of bacteria in nervous tissue.

Table 1 Classification of Lyme neuroborreliosis (LNB)

Early LNB
Neurological symptoms for <6 months
With manifestations confined to PNS (cranial nerves, spinal roots or peripheral nerves) (Bannwarth syndrome)
With CNS manifestations
Late LNB
Neurological symptoms for more than 6 months
With PNS manifestations
With CNS manifestations

PNS, peripheral nervous system.

Early LNB (Table 1)

PNS manifestations. The most common manifestation of early LNB in Europe is a painful meningoradiculitis (Bannwarth's syndrome). The clinical hallmarks of Bannwarth's syndrome are radicular pain (in 86% of the patients) and paresis (in 61%) [3]. The pain is generally described as being of a type never experienced before. The intensity and localization of the pain may vary from day to day and typically exacerbates at night. The paresis may affect muscles innervated by cranial nerves (especially the facial nerve, less often the abducens or the oculomotor nerves), the abdominal wall or the limbs. Headache occurs in about 43%, but a prominent headache without radicular pain or paresis is rare in adults. Apart from Bannwarth's syndrome and lymphocytic meningitis, other peripheral neurological manifestations (in 5–10% of the patients) are plexus neuritis and mononeuritis multiplex.

CNS manifestations. CNS involvement is rare, but patients may present with myelitis or encephalitis. Clinical manifestations like confusion, cerebellar ataxia, opsoclonus–myoclonus, ocular flutter, apraxia, hemiparesis or Parkinson-like symptoms have been associated with *Bb* infection [14]. Poliomyelitis-like syndromes [15], and acute stroke-like symptoms caused by cerebral vasculitis [16] are rare and have been documented only in single case reports.

Late LNB (Table 1)
Late neurological manifestations are also entitled 'chronic neuroborreliosis'.

PNS manifestations. It may consist of mononeuropathy, radiculopathy and polyneuropathy [17,18]. In Europe, late polyneuropathy has only been observed in combination with acrodermatitis chronica atrophicans (ACA) [19] – the typical dermatological manifestation during late stage III of borrelial infection – whilst isolated cases of distal symmetric polyneuropathy as a result of a borrelial infection have been reported in American patients [20]. It is of note that a causative relationship between polyneuropathy and borrelial infection cannot be based on the sole detection of *Bb*-specific antibodies in patients with polyneuropathy as those antibodies can also be found in 5–25% of healthy persons [21].

CNS manifestations. It includes (i) cerebral vasculitis and (ii) chronic progressive Lyme encephalitis or encephalomyelitis with tetraspastic syndrome, spastic–ataxic gait disorder and disturbed micturition [18].

Differences between European and American LNB
Unlike the European Lyme disease, the North American disorder is characterized by erythema migrans, arthritis and meningitis. It is usually deficient of painful radicular symptoms, other cranial nerve involvement besides the facial nerve and ACA.

Paediatric LNB
The most common manifestations of LNB in European children are acute facial nerve palsy (in 55%), other cranial nerve palsies and lymphocytic meningitis (in 27%) [22,23]. Small children may present with unspecific symptoms such as loss of appetite and fatigue. CNS symptoms are rare, but children with early LNB may present with acute myelitis [24], acute hemiparesis [25], opsoclonus–myoclonus [26] or ataxia [27]. Late LNB with chronic hemiparesis has also been reported [25].

Laboratory tests

CSF – inflammatory parameters
European LNB is associated with elevated cell count in the CSF, typically 10–1000 leucocytes/mm^3 [12], mainly lymphocytes and plasma cells. A substantial number of patients have elevated CSF protein and oligoclonal IgG bands [12]. Patients with ACA-associated polyneuropathy often have normal CSF findings. A normal cell count is otherwise rare, but is sometimes present [5], especially in the very early stage, in immunosuppressed individuals and possibly in rare cases of LNB caused by the species *Borrelia afzelii* [5,28]. In such cases, the bacterial pathogen has to be identified by culture or PCR to prove the clinical diagnosis.

Microscope-based assays
Bb can be seen directly in liquid patient material, such as CSF, by applying dark-field microscopy or after staining histological sections [29–31] (class IV), but sensitivity and specificity is low [31]. Focus floating microscopy was recently described as a sensitive method for detection of *Bb* in skin biopsies [32] (class IV).

Recommendations. There is not enough evidence to recommend any of these microscope-based assays as a routine diagnostic tool.

PCR
There are numerous PCR protocols for detection of *Bb* DNA in clinical specimens [1,33,34]. Because of the lack of a gold standard method and lack of large comparative studies, at present it is impossible to recommend a specific PCR protocol. Diagnostic sensitivity of PCR in CSF for early LNB is 10–30% (median). In blood it is even lower [35], and PCR studies in urine are contradictory [1,33,36–38]. In late LNB, sensitivity of PCR is extremely low.

Analytic specificity of PCR (the ability to identify exclusively *Bb* DNA rather than similar DNA) is 98–100% provided precautions are taken to avoid contaminations, and amplified products are specified by an appropriate method, for example sequencing [1,33,35,39]. There are no studies of diagnostic specificity (the ability to correctly identify a person without active infection with a negative test).

Recommendation. PCR on CSF samples has a low sensitivity, but may be useful in very early LNB with negative antibody index (AI), or in patients with immunodeficiency (GPP). Because of low sensitivity and unknown specificity, PCR cannot be recommended as a diagnostic method in patients with chronic symptoms or for follow-up of therapy.

Cultivation
Bb can be recovered from CSF, skin and blood using modified Kelly medium at 30–34°C [40–43]. Cultures should be monitored for up to 12 weeks because of the spirochete's slow growth *in vitro*. As microscopic detection of *Bb* can lead to false-positive readings, spirochete-like structures need to be confirmed as *Bb* by PCR or staining with specific monoclonal antibodies [39,44]. The sensitivity is 10–30% in CSF in early LNB, 50–70% in skin biopsies and $< 10\%$ in blood (erythema migrans).

Recommendation. Because of its low sensitivity, slow growth and restriction to a few specialized laboratories, culture of *Bb* is limited to special indications such as atypical clinical presentation or patients with immune deficiencies (GPP).

Bb-*specific antibodies in serum and CSF*
Bb-specific antibodies in serum can be detected with an IgG- and IgM-differentiating enzyme-linked immunosorbent assay (ELISA) using sonified whole Borrelia, recombinant antigens or single antigens (e.g. VlsE or the C6 peptide) [45–49]. Many laboratories use a two-step approach where sera that are positive in the ELISA screening assay are subjected to immunoblot (IB) for confirmation [39,50–52]. As a confirmatory test, the IB should have an analytic specificity of at least 95%. Diagnostic sensitivity of ELISA screening assays in early LNB is 70–90%, and for late LNB (only IgG, as IgM is not diagnostic for late disease) it is $>$90–100% [45–49] (class III and one class II).

The diagnostic specificity of serum antibody tests are low, because seropositivity in the normal population ranges from 5% to >20% [21,47]. IgM might be false positive as a result of oligoclonal stimulation, and IgG and IgM antibodies may persist for years after successful therapy [6,7]. The diagnostic specificity of C6 ELISA was 61% in one class II study [47]. IB used alone or after a negative ELISA is reported by many laboratories to have a very low specificity. A two-step approach, using WB as a confirmatory assay only on sera that were positive in ELISA, increases the diagnostic specificity according to a class III study [52].

To prove intrathecal production of *Bb*-specific antibodies, calculations that consider blood/CSF-barrier dysfunctions (AI) based on quantitative ELISA are used. Intrathecally produced IgM antibodies show a high sensitivity in LNB of short duration, especially in children [5,53,54]. However, false-positive IgM reactivity has been observed in Eppstein-Barr virus meningitis [53]. In some cases, antibodies are detectable in CSF whilst serum is negative [53]. A positive AI may persist for years after successful therapy [6,7].

Diagnostic sensitivity of the AI is about 80% in LNB of short duration (<6 weeks) [3,4] and nearly 100% in LNB of longer duration, [4,5,39] (class III). Diagnostic specificity was 63% in one class II study [55].

Recommendation. Antibody tests for serum [ELISA or ELISA followed by IB if ELISA is positive (GPP)] and CSF (AI) are useful in the diagnosis of LNB (level B), but are hampered by a low sensitivity in patients with symptom duration <6 weeks, and by low specificity, if judged without other criteria. Because of the low specificity, antibody results can only be interpreted together with clinical data and CSF inflammation parameters. Therefore, antibody testing should only be carried out in patients with symptoms suggestive of LNB.

Chemokine CXCL13

Recent studies have suggested that the B-cell-attracting chemokine CXCL13 is reliably increased in the CSF of patients with well-defined early LNB [38,55–57]. In one class II study, the diagnostic sensitivity of a CXCL13 ELISA in the CSF was 100% in early LNB, the specificity was 63%, and it was normalized in 82% 4 months after treatment [55]. The test might be helpful in seronegative patients during early disease and for control of therapy.

Recommendation. There is not enough evidence to recommend CXCL13 test as a routine diagnostic tool or in follow-up after treatment.

Antigen detection

Assays for antigen detection have been used to detect *Bb* antigens in CSF and in urine samples [58–60]. Limitations include low sensitivity and a poor specificity and reproducibility [61,62].

Recommendation. There is not enough evidence to recommend antigen detection assays as a routine diagnostic tool or in follow-up after treatment.

Detection of antibodies that bind in circulating immune complexes

Sequestration of specific antibodies in immune complexes has been suggested as an important factor for seronegativity in early Lyme borreliosis [63–66]. Results from studies measuring antibodies from dissociated immune complexes are contradictory [63,67]. Detection of immune complexes might be helpful in seronegative patients during early disease.

Recommendation. There is not enough evidence to recommend immune complex tests as a routine diagnostic tool.

Lymphocyte transformation test (LTT)

The aim of the LTT is to detect active Bb infection by testing the cellular immune response. Activation of patient-derived lymphocytes is measured after incubation with Borrelia antigens. Results of studies are contradictory; moreover, there is no relevant study that allows assessment of diagnostic sensitivity and specificity of the tests that are promulgated for diagnosis of Lyme borreliosis [68–72].

Recommendation. There is not enough evidence to recommend LTT as a routine diagnostic tool or in follow-up after treatment.

Cyst formation

So-called 'cysts', spheroplasts or L-forms of *Bb* can be induced *in vitro* by stressors such as high temperature or change in pH [73–76]. Whether or to what extent such forms may have significance for pathogenesis or for the diagnosis of LNB is uncertain.

Recommendation. There is not enough evidence to recommend examination for cyst formation as a diagnostic tool.

CD57+/CD3− lymphocyte subpopulation

There is one study reporting a decreased level of a CD57+/CD3− lymphocyte subpopulation in patients with non-specific symptoms suffering from chronic Lyme [77]. However, the case group was poorly defined,

and the controls inappropriately chosen. Another study found no association between CD57+ and post-Lyme disease symptoms [78].

Recommendation. There is not enough evidence to recommend examination for lymphocyte subpopulations as a diagnostic tool.

Recommendations

Choice of laboratory methods

1. Investigation of CSF/serum pair for *Bb*-specific antibodies, intrathecal antibody production and signs of CSF inflammation is obligatory for laboratory diagnosis of LNB (level B).
2. Culture and PCR may be corroborative in very early LNB (GPP).
3. At present, no further methods are recommendable.

Diagnostic criteria

Lyme neuroborreliosis poses a clinical diagnostic challenge. In view of the variable presentations, diagnostic criteria rooted in a combination of clinical and laboratory findings are necessary. Unfortunately, such criteria, based on international consensus, do not exist. In Europe, detection of intrathecal synthesis of *Bb*-specific antibodies – a positive *Bb* AI – is considered necessary for the diagnosis [79], but its sensitivity can be as low as 55% [4,5,80–84]. American criteria do not require a positive *Bb* AI [85].

We recommend (GPP) the following criteria for definite and possible LNB (Table 2).

Definite LNB. The following three criteria are fulfilled: (I) neurological symptoms suggestive of LNB (with other causes excluded); (II) CSF pleocytosis; (III) *Bb*-specific antibodies in CSF (produced intrathecally).

Table 2 Suggested case definitions for Lyme neuroborreliosis (LNB)

Definite neuroborreliosis[a]	Possible neuroborreliosis[b]
All three criteria fulfilled	Two criteria fulfilled
Neurological symptoms suggestive of LNB without other obvious reasons	
Cerebrospinal fluid pleocytosis	
Intrathecal *Bb* antibody production	

[a]These criteria apply to all subclasses of LNB except for late LNB with polyneuropathy where the following should be fulfilled for definite diagnosis: (I) peripheral neuropathy (II) acrodermatitis chronica atrophicans (III) *Bb*-specific antibodies in serum.
[b]If criteria III is lacking; after a duration of 6 weeks, there have to be found *Bb*-specific IgG antibodies in the serum.

Possible LNB. Two out of these three criteria are fulfilled. If criterion III is lacking; after a duration of 6 weeks, there has to be found *Bb*-specific antibodies in the serum.

These criteria apply to all subclasses of LNB except for late LNB with polyneuropathy where the following should be fulfilled for definite diagnosis:
(I) Peripheral neuropathy
(II) Clinical diagnosis of ACA
(III) *Bb*-Specific antibodies in serum.

Treatment

Early LNB

Early LNB with manifestations confined to the PNS and meninges

Effective agents. In 1983, two class IV, small case series indicated the effect of high dose intravenous (IV) penicillin [86,87]. Several class III and IV studies have reported response to 10- to 28-day courses of IV penicillin (20 million U daily), IV ceftriaxone (2 or 4 g daily), IV cefotaxime ($3\text{ g} \times 2\text{ g}$ or $2\text{ g} \times 3\text{ g}$ daily) and oral doxycycline (200 mg daily for 2 days and 100 mg daily for 8 days) [14,88–91] (Table 3). IV ceftriaxone, cefotaxime and penicillin seem to have similar efficacy [88,90,91] (class III). First-generation cephalosporins were ineffective *in vitro* against *Bb* in an American study [92]. There are not enough data to support the use of the following: metronidazole, trimetoprim-sulfamethoxazole, fluconazole, isoniazid, combinations of antibiotics or steroids.

Oral versus intravenous administration of antibiotics. Oral doxycycline has a good CSF penetration and gives CSF concentrations above the minimum inhibitory concentration [93]. Several class III studies have shown that oral doxycycline has similar short- and long-term efficacy as have various parenteral regimens [89,94–98]. A recent Norwegian class I study of 102 LNB patients showed that oral doxycycline (200 mg daily for 14 days) was non-inferior if compared with IV ceftriaxone (2 g daily for 14 days) [11].

Duration of treatment. The occurrence of persistent residual symptoms after standard antibiotic therapy has led to speculations about surviving bacteria and an eventual need for longer treatment duration. There are no class I comparisons of different treatment durations. In most European treatment studies, the duration ranged from 10 to 14 days (Table 3), and few studies for as long as 28 days. A case series reported excellent or good response in 90% of patients with disseminated Lyme

Table 3 Inclusion criteria and clinical outcome results of treatment trials for adult Lyme neuroborreliosis

First author, year	Inclusion criteria	Response criteria	Disease duration[a]	Treatment	Response rate	Remarks
Dattwyler, 1988 [88]	Physician observed EM or ELISA and two organ manifestations	Absence of arthritis, neurophysiologic findings and encephalopathy	35 mo 28 mo 29 mo 39 mo	IV Penicillin 10 d vs. IV Ceftriaxone 2 g 14 d and IV Ceftriaxone 2 g vs. IV Ceftriaxone 4 g	5/10 12/13 13/14 14/17	Half of the patients had received oral antibiotics. Class III
Kohlhepp, 1989 [14]	ELISA and three of: TB/EM, radicular pain, radiculitis, arthritis/carditis/neurological findings, meningitis, cranial neuritis	Complete recovery at 12 mo	4 mo 5 mo	IV Doxycycline 10 d (n = 39) vs. IV Penicillin 10 d (n = 36)	2/3 in both groups	10 patients were retreated. Class III
Pfister, 1989 [90]	Bannwarth syndrome or meningitis with TB or EM and ELISA	Normal neurological findings at 7.7 mo	29 d 24 d	IV Penicillin 10 d vs. IV Cefotaxime 10 d	8/10 9/11	Class III
Hassler, 1990 [89]	ELISA and arthritis, neuropathy or ACA lasting at least 6 mo	Absence of symptoms within 6 mo and persisting remission in 24 mo	>6 mo	IV Cefotaxime 8–10 d vs. IV Penicillin 8–10 d	44/69 25/66 P = 0.002	Class III
Logigian, 1990 [17]	Previously signs of LD, neurological symptoms ≥3 mo and immunity to *Bb*	Neurological improvement at 6 mo	12 mo	Iv Ceftriaxone 14 d	17/27	Half of the patients had received oral or IV antibiotics. Class IV
Pfister, 1991 [91]	Bannwarth syndrome or meningitis with ELISA	Normal neurological findings at mean 8.1 mo after therapy	33 d 32 d (median) 3.5 w	IV Ceftriaxone 10 d vs. IV Cefotaxime 10 d	8/12 9/15	Class III
Karlsson, 1994 [97]	Meningoradiculitis, encephalomyelitis or chronic meningitis and CSF pleocytosis and positive ELISA or cultivation	Complete recovery at 12 mo	4 w (median)	IV Penicillin 14 d vs. O Doxycycline 14 d	18/21 27/30	2 patients were retreated. Class III
Dotevall, 1999 [95]	Facial palsy, CSF pleocytosis and ELISA or EM	Complete recovery at 6 mo	23 d	O Doxycycline 9–17 d	26/29	Class IV
Karkkonen, 2001 [96]	Bannwarth syndrome or encephalomyelitis, CSF pleocytosis and ELISA or EM	Complete recovery at 1 year and improvement at 1 year	4 w (median)	O Doxycycline 10–28 d	56/69 69/69	6 patients were retreated. Class IV
Borg, 2005 [94]	Clinical neuroborreliosis, CSF pleocytosis and one of EM, intrathecal antibody production, isolation of Borrelia or seroconversion	Complete recovery at 6 mo	21 d 28 d (median)	IV Ceftriaxone 10–14 d vs. O Doxycycline 10–14 d	23/29 26/36	Class III
Ogrinc, 2006 [98]	Neurological symptoms, no CSF pleocytosis, ELISA or EM	Clinical improvement at 12 mo	18 mo (median)	O Doxycycline 28 d (n = 23) vs. IV Ceftriaxone 14 d + PO Doxycycline 14 d (n = 23)	74% 70%	Class III
Dattwyler, 2005 [88]	Objective organ manifestations of at least 3 mo duration, EM or exposure to endemic area and ELISA and WB	Complete recovery/ treatment failures	>3 mo	IV Ceftriaxone 14 d (n = 65) vs. IV Ceftriaxone 28 d (n = 43)	76%/6% 70%/0%	Many drop outs. Half of the patients had received oral antibiotics. Class III

Table 3 (Continued)

First author, year	Inclusion criteria	Response criteria	Disease duration[a]	Treatment	Response rate	Remarks
Oksi, 2007 [99]	Clinical disseminated Lyme borreliosis (of them 62 neuroborreliosis) confirmed by ELISA, PCR or culture	VAS < 30	?	IV Ceftriaxone 21 d followed by O Amoxicillin in 100 d vs. placebo in 100 d	49/52 47/54	Class II
Ljøstad, 2008 [11]	Neurological symptoms and one of: CSF pleocytosis, intrathecal antibody production or ACA	Improvement on a composite clinical score at 4 mo	10 w 8 w	O Doxycycline 14 d (n = 54) IV Ceftriaxone (n = 48)	4.5 units 4.4 units P = 0.84	Class I

d, days; w, weeks; mo, months; ACA, acrodermatitis chronica atrophicans; CSF, cerebrospinal fluid; ELISA, *Bb* antibodies detected by ELISA method; EM, erythema migrans; IV, intravenous; LD, Lyme disease; O, oral; TB, tick bite; VAS, visual analogue scale; WB, *Bb* antibodies detected by Western blot.
[a]Pre-treatment disease duration.

(including neuroborreliosis) after treatment with oral cefixime or IV ceftriaxone for 14 days followed by oral amoxicillin for 100 days [99] (class IV). However, a Finnish class II study showed no benefit of extended treatment [100]. In this study, 152 patients with disseminated Lyme disease (including 62 with neuroborreliosis) were randomized to treatment of 3 weeks with IV ceftriaxone followed by either oral amoxicillin (2 g b.i.d.) or placebo for 100 days. At 1-year follow-up, the groups were similar with about 90% having excellent or good outcome.

Recommendations. Adult patients with definite or possible early LNB with symptoms confined to the meninges, cranial nerves, nerve roots or peripheral nerves (Bannwarth syndrome) should be offered a single 14-day course of antibiotic treatment.
1. Oral doxycycline or IV ceftriaxone or IV penicillin or IV cefotaxime are effective and safe treatments (level B).
2. Oral doxycycline (200 mg daily) and IV ceftriaxone (2 g daily) for 14 days are equally effective (level A). The advantages of doxycycline are the oral route of administration and the lower costs. Doxycycline is relatively contraindicated during pregnancy or lactation.

Early LNB with CNS symptoms
Whether early LNB with CNS manifestations (encephalitis, myelitis or vasculitis) should be treated different from Bannwarth syndrome is uncertain. Case studies suggest good recovery with IV ceftriaxone for 2–3 weeks [15,101–104] (class IV). In a Swedish Slovenian comparative study of IV ceftriaxone and oral doxycycline, two of 29 patients in the ceftriaxone group and three of 36 in the doxycycline group had encephalitis. All patients were reported to improve after treatment [94] (class III).

Recommendations. Adult patients with definite or possible early LNB with CNS manifestations (myelitis, encephalitis, vasculitis) should be treated with IV ceftriaxone (2 g daily) for 14 days (not enough evidence: GPP).

Late LNB

Effective agents
There are no randomized treatment studies of European late LNB. Small subgroup analyses and case studies indicate the effect of IV ceftriaxone (2 g daily) given for 2–4 weeks, or IV penicillin (20 million U daily for 10 days) or doxycycline (200 mg daily) [16,91,101,105] (class IV). An American study showed better effect of ceftriaxone than penicillin [88] (class III). There are not enough data to support the use of steroids alone or in combination with antibiotics.

Oral versus intravenous administration of antibiotics
Subgroup analysis of 10 patients with late LNB in a class I comparative Norwegian study showed equal improvement after 14 days of oral doxycycline as after 14 days of IV ceftriaxone [11] (class III). In a Swedish study of late LNB with peripheral neuropathy and ACA, improvement in neurological symptoms was similar in 26 patients who received oral doxycycline for 3 weeks, as in 21 who received IV penicillin for 2 weeks followed by oral doxycycline for 2 weeks [19] (class III).

An European open-label study of late Lyme borreliosis (defined as non-specific CNS symptoms, but without CSF pleocytosis or other neurological findings, and therefore not convincing LNB) showed similar improvement rates 6 months after treatment with 4 weeks of oral doxycycline versus 2 weeks of IV ceftriaxone followed by 2 weeks of oral doxycycline (59% vs. 67%) [98] (class III).

Duration of treatment
There are no comparative controlled studies of treatment length in European late LNB. A recent American open-label randomized comparison (class III) of 14-day vs. 28-day treatment with ceftriaxone (2 g daily) for late Lyme borreliosis (143 patients, of whom a third with neurological symptoms) showed similar cure rates (76% and 70%, respectively) after 1 year, and there were more discontinuations as a result of adverse events in the 28-day group [106]. Another series (class IV) of late LNB showed disappearance of symptoms in 69/79 (87%) after 100 days regimens with various antibiotics, whereas 14 days with ceftriaxone cured four of 13 (31%) [107].

Recommendations
1. Adult patients with definite or possible late LNB with peripheral neuropathy and ACA should be treated with oral doxycycline (200 mg daily) or IV ceftriaxone (2 g daily) for 3 weeks. (not enough evidence: GPP).
2. Adult patients with definite or possible late LNB with CNS manifestations (myelitis, encephalitis, vasculitis) should be treated with IV ceftriaxone (2 g daily) for 3 weeks. (not enough evidence: GPP).

Clinical course after treatment

Most studies report marked improvement in objectively demonstrable neurological abnormalities within weeks to a few months after 10–14 days of antibiotic treatment. However, symptoms and mild pleocytosis may persist for several months. Relapses or treatment failures (defined as loss of significant improvement) are very rare.

Disabling neurological sequels were found in 12% of patients after 12 months of follow-up [108], and in 5% after 33 months of follow-up [3]. They were more frequent in patients with CNS manifestations or long duration of symptoms before treatment [8,10,24,41,43,52] (class III). Persistent or new subjective complaints (concentration problems, memory problems, headache, fatigue, myalgias and paraesthesias) may be more common [109,110] (class IV). When taking both objective and subjective complaints into consideration, complete recovery was achieved in 41% of patients after 4 months [11], in 61–72% after 6–9 months [94,108], in 50–70% after 12 months [14,108,110] and in 50–90% after 5 years [97,108–110]. However, the studies are hampered by ill-defined outcome measures and lack of control groups. One Swedish study found persistent complaints 2.5 years post-treatment in 50% of patients who had experienced neuroborreliosis when compared to 16% in control patients who had experienced erythema migrans [111].

Post-Lyme disease syndrome (PLDS)

If subjective complaints or symptoms (such as fatigue, paraesthesias, difficulty in sleeping, cognitive impairment, headache, arthralgia and myalgia) persist for more than 6 months after standard treatment of LNB or other clearly defined Lyme disease manifestations, the condition is often termed PLDS [112].

American trials have demonstrated that additional prolonged antimicrobial treatment is ineffective in PLDS [113–116]. A regimen of IV ceftriaxone for 30 days followed by 60 days of oral doxycycline was not more beneficial than placebo on health-related quality of life as measured by SF-36 [115] (class I) or cognitive functioning [114] (class II) in 78 seropositive and 51 seronegative PLDS patients. Of noteworthy, placebo-treated patients had a 36% improvement on SF-36 scores. Another class I study [116] of 55 patients randomized to receive a 28-day course of IV ceftriaxone or IV placebo showed a higher reduction in fatigue score in the ceftriaxone group after 6-month follow-up, but the groups did not differ in the other primary end-point (mental speed) or in secondary end-points (such as a scale for fatigue and pain, SF 36, self-reported depression and various cognitive functions). Four severe adverse events occurred, one case of anaphylaxis (the ceftriaxone group) and three cases of sepsis (placebo group). The effect on fatigue may have been a result of placebo effect, as more patients in the ceftriaxone group guessed their correct assignment. In the most recent study [113] (class I), a small selection of PLDS patients with objective memory impairment (encephalopathy) were randomized to 10 weeks of IV ceftriaxone (23 patients) or placebo (14 patients) and compared with 18 healthy control patients. At week 12,

there was a moderate improvement on a calculated aggregate of neuropsychological measures in favour of the ceftriaxone-treated patients, but the effect was not sustained to week 24.

Recommendations
Antibiotic therapy has no impact on PLDS (level A).

Paediatric neuroborreliosis

One Austrian class II study suggests similar effect of 14 days of IV penicillin when compared to 14 days of IV ceftriaxone in acute paediatric LNB [117]. Several European class III and IV studies suggest good response to 10- to 14-day courses of IV penicillin, ceftriaxone, cefotaxime and oral doxycycline [3,53,118,119]. There is no data to suggest better response to IV than oral treatment. However, doxycycline in most countries is not recommended in children under 8 years of age (9 in some countries) as it may cause staining of the teeth. Nevertheless, recent data suggest that this may be less common than previously thought and that it can be prevented by avoiding sunlight [120,121]. There is no data to suggest treatments duration longer than 14 days in paediatric patients with CNS manifestations or late LNB.

As in adults, 11–22% of paediatric LNB patients have neurological sequelae (mostly facial palsy) after treatment [23,119]. A recent prospective follow-up study of 177 Swedish children demonstrated that LNB-persisting unspecific symptoms (mainly headache and fatigue) at 6 months were not more frequent in patients than in controls. Another Swedish series of 203 children with LNB treated for 10 days with IV penicillin (53), ceftriaxone (109), cefotaxime (19) or oral doxycycline (22) showed resolution of symptoms and signs in 58% by the end of treatment, in 92% by 2 months and in 100% by 6 months [119] (class IV).

In an American study of 43 children with facial palsy attributable to Lyme and treated with IV ceftriaxone (16%) or oral doxycycline or amoxicillin (84%), 79% reported to be cured after an average of 49-month follow-up. The frequency of self-reported problems with normal daily activities was similar in patients and age-matched controls [122].

Recommendations
Paediatric patients with definite or possible early LNB with symptoms confined to the meninges, cranial nerves, nerve roots or peripheral nerves (Bannwarth syndrome) should be offered a single 14-day course of antibiotic treatment.
1. Oral doxycycline or IV penicillin or IV ceftriaxone or IV cefotaxime is effective and safe treatments (level B).
2. Oral doxycycline (200 mg daily) and IV ceftriaxone (2 g daily) for 14 days are equally effective (level B). The advantages of doxycycline are the oral route of administration and the lower costs. Doxycycline is contraindicated in those <8 years (in some countries 9 years).
3. Paediatric patients with CNS manifestations (myelitis, encephalitis, vasculitis) should be treated with IV ceftriaxone (2 g daily) for 14 days (not enough evidence: GPP).

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Conflicts of interest

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For a full list of References, please see Reference Appendix pp. e1–e4.

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