Lyme borreliosis: diagnosis and management

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ABSTRACT

Lyme borreliosis is the most common vectorborne disease in the northern hemisphere. It usually begins with erythema migrans; early disseminated infection particularly causes multiple erythema migrans or neurologic disease, and late manifestations predominantly include arthritis in North America, and acrodermatitis chronica atrophicans (ACA) in Europe. Diagnosis of Lyme borreliosis is based on characteristic clinical signs and symptoms, complemented by serological confirmation of infection once an antibody response has been mounted. Manifestations usually respond to appropriate antibiotic regimens, but the disease can be followed by sequelae, such as immune arthritis or residual damage to affected tissues. A subset of individuals reports persistent symptoms, including fatigue, pain, arthralgia, and neurocognitive symptoms, which in some people are severe enough to fulfil the criteria for post-treatment Lyme disease syndrome. The reported prevalence of such persistent symptoms following antimicrobial treatment varies considerably, and its pathophysiology is unclear. Persistent active infection in humans has not been identified as a cause of this syndrome, and randomized treatment trials have invariably failed to show any benefit of prolonged antibiotic treatment. For prevention of Lyme borreliosis, post-exposure prophylaxis may be indicated in specific cases, and novel vaccine strategies are under development.

Introduction

Lyme borreliosis, or Lyme disease, is an emerging tickborne disease, primarily caused by the bacterium Borrelia burgdorferi sensu stricto (ss) in North America and predominantly Borrelia afzelii or Borrelia garinii in Europe. Reported incidence has been increasing, and the clinical manifestations of Lyme borreliosis are diverse. Establishing the diagnosis may be complex, particularly for early manifestations, before a serological response has developed, and where there is disseminated infection in the joints, the heart, or the central nervous system. Another limitation of serological testing is that antibodies can remain for years after infection, and serology can therefore not be used to assess the efficacy of antibiotic therapy. Thus, the diagnosis and evaluation of Lyme borreliosis mainly depends on clinical evaluation, as is discussed in this review. Most people respond well to antibiotic therapy as recommended by treatment guidelines. However, some report post-infectious signs or symptoms, despite recommended antibiotic therapy and putative clearance of infection. These symptoms, which include fatigue, pain, and neurocognitive symptoms, may be persistent and highly disabling. Common uncertainties among patients and physicians include the reliability of diagnostic tests for Lyme borreliosis, and the pathogenesis and therapy of persistent symptoms.

In this review, we assess the diagnostic and therapeutic approach to Lyme borreliosis, and the evidence related to pathogenesis and management of sequelae and post-infectious symptoms attributed to Lyme borreliosis.

Sources and selection criteria


We categorized human, animal, and in vitro studies based on title and abstract into the topics of this review, and favored randomized trials, systematic reviews, and guidelines in English. Observational patient studies, in vitro, and animal studies with adequate study design and statistical methods were also reviewed. Because of the clinical focus of this review, we also included case series.

We also reviewed clinical trials of limited quality and correspondence to describe actual controversies. Studies published before 2009 were included if they were referred to by selected papers, guidelines, or reviews. We included articles of sufficient quality published after January 2019 (during the writing...
Incidence and epidemiology

*Borrelia burgdorferi* sensu lato and their vectors

Lyme borreliosis is caused by spirochetes belonging to the *Borrelia burgdorferi* sensu lato (sl) complex, which consists of ~20 genospecies with a complex genomic structure. Not all *B. burgdorferi* sl species are pathogenic, and in North America, *Borrelia burgdorferi* ss is the dominant genospecies associated with Lyme borreliosis, although a novel genospecies, *Borrelia mayonii*, was recently identified. In Eurasia, *B. afzelii* and *B. garinii* are the most common *B. burgdorferi* sl genospecies in ticks and humans. *B. burgdorferi* sl genospecies are genetically distinct from other species within the genus *Borrelia*—ie, those causing relapsing fever. Recently, it was suggested to divide the genus *Borrelia* into two, with the new genus name for the Lyme borreliosis group of spirochetes being *Borreliella*, although it is debatable whether such a split is justified.

*B. burgdorferi* sl spirochetes are transmitted through the bite of tick species belonging to the genus *Ixodes*, which are largely confined to temperate climate zones of the northern hemisphere. In North America, the *Ixodes* species that transmits the causative agent of Lyme borreliosis is primarily *Ixodes scapularis*; however, *Ixodes pacificus* also acts as a vector in the western coastal regions. In Europe, *Ixodes ricinus* is the tick species primarily responsible for transmitting *B. burgdorferi* sl, whereas *Ixodes persulcatus* is predominant in large parts of Russia and Asia. On average, in Europe 12% of nymphal and 15% of adult *I. ricinus* ticks are infected with *B. burgdorferi* sl, and 2-3% of humans develop Lyme borreliosis after a tick bite, which is similar to the incidence in the US.

Incidence of Lyme borreliosis in the northern hemisphere

In 2006 roughly 85 000 cases of Lyme borreliosis were reported annually in Europe, and more recently, this was estimated to be approximately 230 000 in Western Europe, although this is thought to be an underestimate. Incidences in some countries peak as high as 350 per 100 000 population and have increased in the past two decades. Lyme borreliosis is also highly prevalent in North America; the number of reported cases has gradually increased over time in the US, and the Centers for Disease Control and Prevention (CDC) has estimated that there are more than 300 000 new cases each year. The causes for this increase include greater abundance of wildlife hosts on which ticks feed and propagate, and climatic changes, which result in expansion of the latitude, altitude, and seasonality at which ticks are found. This increase has led to a substantial disease burden and economic costs, and has brought societal and political concerns in both the US and Europe.

Clinical manifestations and diagnosis

Below we describe the most common clinical disease manifestations in Europe and North America in children and adults. The clinical spectrum is more diverse, but rare disease manifestations are beyond the scope of this review. The diagnostic strategies for Lyme borreliosis are reviewed in box 1 and table 1.

Cutaneous manifestations

**Erythema migrans**

Erythema migrans, the most common manifestation of Lyme borreliosis, is characterized by a red or bluish-red macular skin lesion expanding over the course of days to weeks (fig 1). In contrast, a tick bite rash may develop within hours to days and generally fades after several days. Only half of people diagnosed with erythema migrans recall a tick bite. Historically, a typical case of erythema migrans has been characterized by a bright red outer border with central clearing. However, *B. burgdorferi* ss and *B. garinii* usually lead to homogeneous erythema migrans, as opposed to *B. afzelii* erythema migrans, which is characterized by central clearing in 60% of cases. In 2-18% of cases, erythema migrans is multiple. Untreated erythema migrans may persist for several weeks and occasionally months.

**Borrelial lymphocytoma**

Borrelial lymphocytoma is a rare skin manifestation characterized by a painless bluish-red nodule, which is predominantly reported in children. Typically, borrelial lymphocytoma is localized on the ear lobe, nipple, or scrotum. Often, there is a preceding or concomitant erythema migrans. With antibiotics, borrelial lymphocytoma is usually cleared within several weeks.

**Acrodermatitis chronica atrophicans**

Acrodermatitis chronica atrophicans (ACA) is reported in 1-3% of Lyme borreliosis cases in Europe, and is predominantly caused by *B. afzelii*. ACA manifests as a chronic, slowly progressive red or bluish skin lesion, which eventually may become atrophic. ACA is a late manifestation of Lyme borreliosis, and may present several months to years after an untreated erythema migrans. It has been postulated that ACA does not resolve spontaneously, in contrast to most other manifestations of Lyme borreliosis. Indeed, even lesions present for 10 years may reveal active infection by culture or PCR positivity, and respond to antimicrobial therapy. Concurrent peripheral neuropathy is common, and local joint involvement may occur.

**Nervous system manifestations**

Dissemination of *Borrelia* spp primarily involves the skin, nervous system, joints, or, more rarely, the heart. Neurologic manifestations, henceforth called Lyme neuroborreliosis, are reported in ~10% of all cases of Lyme borreliosis. Early Lyme neuroborreliosis usually presents days to weeks...
The neurological complications of Lyme borreliosis are described in this text. It is characterized by a mononeuropathy multiplex, causing a wide variety of peripheral nerve disorders. Cranial neuritis, or radiculoneuritis, may be bilateral in up to 25% of individuals. Only sporadic cases of chronic encephalitis or Lyme arthritis have been reported.

### Laboratory Support for Diagnosis of Lyme Borreliosis

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Sensitivity and Specificity</th>
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<tbody>
<tr>
<td>Serology</td>
<td>High yield*</td>
</tr>
<tr>
<td>Polymerase chain reaction</td>
<td>Reasonable sensitivity on skin and synovial samples, low sensitivity on cerebrospinal fluid*</td>
</tr>
<tr>
<td>Cerebrospinal fluid (CSF) analysis</td>
<td>Similar to PCR, CSF cultures for Borrelia spp have a low yield*</td>
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</tbody>
</table>

**Box 1:** Laboratory support for diagnosis of Lyme borreliosis

**Serology**
- Most readily available form of laboratory support. Should be interpreted in combination with the clinical symptoms and signs.
- Two-tier testing is typically performed, where equivocal or positive ELISA based screening test results are technically confirmed using a second test, which can be another ELISA, western blot, or immunoblot.
- Clinical signs often precede an antibody response. Therefore, in early phases of the disease, antibody responses may be absent, but sensitivity increases over time.
- Absence of antibody response has been reported in cases confirmed by polymerase chain reaction (PCR) or culture.
- Antibiotic therapy may abort serologic response or prevent seroconversion.
- Background seroprevalence exists, from 5% in the general population in endemic regions to 50% in hunters.
- Serum Borrelia IgG may persist for decades. Therefore, serology cannot be used to monitor disease activity or eradication.

**Polymerase chain reaction**
- Reasonable sensitivity on skin and synovial samples, low sensitivity on cerebrospinal fluid.*
- In other materials, such as blood or urine, PCR has no or limited diagnostic value.
- Limited utility in monitoring treatment response, as Borrelia DNA may be detected after successful antibiotic treatment.

**Cerebrospinal fluid (CSF) analysis**
- Similar to PCR, CSF cultures for Borrelia spp have a low yield.*
- Diagnosis relies on indirect measures of meningeal inflammation: pleocytosis, intrathecal antibody production.
- Intrathecal Borrelia antibody is measured by calculating the CSF:serum antibody index and has been shown to persist for years after successful treatment, and thus cannot be used to monitor treatment.
- Chemokine C-X-C motif ligand 13 (CXCL13) is an early biomarker and its concentration falls rapidly after initiation of antibiotic therapy. Elevated CXCL13 concentrations in CSF may also be detected in other disorders, particularly neurosyphilis and central nervous system lymphoma.

**Cellular immune response tests and other non-recommended tests**
- Based on assessing T cell mediated immune responses following in vitro stimulation by a specific pathogen. Interferon gamma based cellular tests are well established for tuberculosis, but experimental for Lyme borreliosis.
- In Lyme borreliosis, results are inconsistent because of small patient cohorts, no clear case definitions, no or poorly defined control groups, and lack of independent academic validation.
- In a small cohort study, the sensitivity of a cellular assay measuring IFN-γ release was suggested to exceed that of serology during early infection.
- Validation of four cellular assays in larger populations with early Lyme borreliosis is ongoing.
- A variety of commercially available testing methods, including urine antigen testing, quantitative CD57 assay, or dark field microscopy on blood, lack a solid scientific basis as well as independent, reproducible validation and should be avoided for clinical use.

*Sensitivity and specificity are reported in table 1.

**Lyme arthritis**
Lyme arthritis typically presents as an oligo- or monoarthritis, often involving the knee joint, three to six months after infection. In contrast to other causes of septic arthritis, Lyme arthritis usually is less painful and not accompanied by fever. Most patients do not report a preceding tick bite or erythema migrans.
**Table 1 | Diagnostic tests for Lyme borreliosis**

<table>
<thead>
<tr>
<th>Manifestations</th>
<th>Serology</th>
<th>PCR</th>
<th>Culture</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>Erythema migrans (EM)</td>
<td>Sensitivity (%)</td>
<td>Specificity (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Summary sensitivity</td>
<td>50 (95% CI 40 to 61)</td>
<td>95 (95% CI 92 to 97)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>30-89</td>
<td>98-100</td>
<td>100</td>
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<tr>
<td>Specificity (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>78 (95% CI 79 to 99)</td>
<td>95 (95% CI 75 to 99)</td>
<td>95 (95% CI 92 to 95)</td>
<td>Specificity is approximately 95% (95% CI 75 to 99%) in case-control studies and approximately 80% (95% CI 40 to 95%) in cross sectional studies. Background seroprevalence is an important confounder in the latter study design. Specificity of two tier testing is generally higher than one tier testing PCR assay. In a recent large study sensitivity was 77.7% (n=123). Median sensitivity was higher in European than in US studies. EM is a clinical diagnosis. PCR is mostly used in research or in atypical cases. In such cases, histological findings may also support the diagnosis.12</td>
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</table>

**Culture:** In a European study, 55.1% of biopsies were culture positive, of which 98.8% B. afzelii, and 3.2% B. garinii. Sensitivity of large volume cultures from EM patients in the US, of whom 30% had multiple EM, was 44%.53

<table>
<thead>
<tr>
<th>Borrelial lymphocytoma</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
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<tbody>
<tr>
<td>Summary sensitivity</td>
<td>98 (95% CI 84 to 100)</td>
<td>94 (95% CI 90 to 97)</td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>Range</td>
<td>20-100</td>
<td>20-67</td>
<td>100</td>
<td></td>
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<tr>
<td>Specificity (%)</td>
<td></td>
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<td>100</td>
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<td></td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>Serology: Most cases had serum anti-B. burgdorferi IgG antibodies (with or without IgM antibodies).14 Higher seropositivity rates were observed in more recent studies (2001-14 vs 1986-2000), most likely owing to more sensitive diagnostic tests.54,55</td>
</tr>
</tbody>
</table>

Specificity as described for erythema migrans PCR assay: In this study, the diagnosis was based on clinical and pathological criteria and samples were formalin fixed and paraffin embedded, which could have impaired sensitivity. Histological findings may support the diagnosis.57

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**Acrodermatitis chronica atrophicans (ACA) | Sensitivity (%) | Specificity (%) | | |
<table>
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<tr>
<td></td>
<td>67</td>
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<td>67</td>
<td>Serology: Mostly IgG antibodies, occasionally IgM antibodies, were found. High quality case-control studies reported average sensitivity of 98%.48 PCR assay: median sensitivity 75%.69 Studies restricted to Europe, as ACA is associated with B. afzelii. Histological findings may support the diagnosis.57</td>
</tr>
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</table>

Because of limited number of studies, median sensitivity and specificity is reported

PCR assay (synovial fluid/tissue): For Lyme arthritis, PCR is an important tool. Sensitivity in synovial tissue was higher than in synovial fluid.45 PCR did not discriminate between residual DNA and viable organisms.54,60

Culture (synovial fluid/tissue): Cultivation of B. burgdorferi from synovial fluid is generally unsuccessful, but may reveal non-motile spirochetes.61

<table>
<thead>
<tr>
<th>Lyme neuroborreliosis</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
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<tbody>
<tr>
<td>Summary sensitivity</td>
<td>78 (95% CI 53 to 92)</td>
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<td>100</td>
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<tr>
<td>Range</td>
<td>5-17</td>
<td>99-100</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Specificity (%)</td>
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<td>100</td>
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</table>
| | 67 | 67 | 67 | For a definite diagnosis of Lyme neuroborreliosis, three of the following criteria should apply: 1. Neurologic signs compatible with Lyme neuroborreliosis; 2. CSF pleocytosis, defined as >5 cells ×10^9/L; 3. Intrathecal production of antibodies.66 For a probable diagnosis, two criteria should be met66

Serology: Sensitivity 95% CI was 41 to 92%;68 Intrathecal antibody synthesis (CSF): Average sensitivity was ~80% (95% CI 94 to 99%).49 Sensitivity in US patients 87%;50 compared with European patients 56-79%.65,66 In early cases, intrathecal antibodies may still be absent; at 6-8 weeks after onset of symptoms, specific IgG production is expected to be detectable in all patients.70

Other non-specific signs of inflammation in CSF, such as elevated total protein level or intrathecal synthesis of total IgM, IgG, or IgA, may also be present.70

PCR assay (CSF): Median sensitivity was 22.5%, and lower in European than in US studies49

CXCL13 (CSF): In a European meta-analysis, a pooled sensitivity of 85-93% and pooled specificity of 92-98% was found using an optimal cut-off value of 162 pg/mL.47 Elevated CXCL13 may also be a result of CNS infection or malignancy.71,72 CXCL13 correlates with intrathecal B. burgdorferi antibody response in acute Lyme meningitis.71,72

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Lyme carditis
During early disseminated infection, acute cardiac involvement may occur, characterized by atrioventricular conduction defects in varying degrees. Less common cardiac manifestations include acute myopericarditis or, rarely, cardiomyopathy. Lyme carditis usually is self-limited, but is potentially fatal if untreated. Most case series on the relation between carditis and Lyme borreliosis lack causality; however, selected studies have identified *B. burgdorferi* in endomyocardial biopsy samples from patients with dilated cardiomyopathy.

Differences between clinical manifestations in North America and Europe
The differences in *Borrelia* genospecies between the continents result in differences in clinical presentation. In North America, central clearing of erythema migrans is uncommon: up to 18% of erythema migrans cases are multiple, and Lyme borreliosis is more often associated with constitutional symptoms, such as fever and malaise. *B. burgdorferi* ss in North America is more arthritogenic, and Lyme arthritis is more frequently encountered in North America (28% of Lyme borreliosis cases) than in Europe (3-7%). Lyme neuroborreliosis in North America mostly presents as subacute meningitis with or without cranial neuropathy (usually facial palsy), and less frequently as painful radiculoneuritis. In Europe, *B. garinii* is particularly neurotropic, and typically associated with painful radiculoneuritis and lymphocytic meningitis (originally described as Bannwarth syndrome). *B. afzelii* primarily causes skin infections, including ACA and borrelial lymphocytoma, both of which are virtually absent in North America with constitutional symptoms, such as fever and malaise. *B. burgdorferi* ss in North America is more arthritogenic, and Lyme arthritis is more frequently encountered in North America (28% of Lyme borreliosis cases) than in Europe (3-7%). Lyme neuroborreliosis in North America mostly presents as subacute meningitis with or without cranial neuropathy (usually facial palsy), and less frequently as painful radiculoneuritis. In Europe, *B. garinii* is particularly neurotropic, and typically associated with painful radiculoneuritis and lymphocytic meningitis (originally described as Bannwarth syndrome). *B. afzelii* primarily causes skin infections, including ACA and borrelial lymphocytoma, both of which are virtually absent in North America.
spread transplacently, and evidence for congenital infection has indeed been reported in a few cases where *Borrelia* species were cultured from the newborn post mortem. A meta-analysis of nine studies suggested fewer adverse birth outcomes in women who were treated for gestational Lyme borreliosis compared with untreated cases, suggesting indirect evidence for adverse birth outcomes. Conversely, untreated ACA during pregnancy, an active chronic infection, was not associated with adverse outcomes in a retrospective survey, and in a systematic review, eight epidemiological studies reporting on potential associations between *Borrelia* sl exposure and adverse birth outcomes did not suggest any relation.

**Treatment**

**Early localized/disseminated disease**

For treatment of erythema migrans, doxycycline, amoxicillin, and oral cephalosporins were equally effective in randomized clinical trials, with complete response rates >90%. Azithromycin was as effective as doxycycline or amoxicillin in European open label trials, but not in a randomized double blind controlled study in 246 patients in North America. As a result, doxycycline generally is regarded first choice therapy for erythema migrans. Randomized trials have shown that doxycycline for a duration of 10 days is as effective as 15 or 21 days. Persistent symptoms after treatment were no more frequent in patients treated for ≤10 days as compared with longer courses in a retrospective cohort study with a mean follow-up duration of 2.9 years. For multiple erythema migrans, oral doxycycline for 14 days has been shown to be as effective as intravenous ceftriaxone in an open label alternate treatment trial among 200 patients.

**Lyme neuroborreliosis**

Lyme neuroborreliosis is typically treated with intravenous ceftriaxone for at least 14 days. After meningoradiculitis, clinical recovery often is slow, and neurologic sequelae or subjective symptoms may persist in up to 40-50% of patients after 30 months. While no studies have assessed the optimal duration of ceftriaxone therapy, the slow clinical resolution and long term neurologic sequelae have led some clinicians to extend the duration of treatment to up to 28 days. In a prospective, double blind study in Europe of 102 adults with early Lyme neuroborreliosis, oral doxycycline was found to be as effective as ceftriaxone. Long term outcomes (neurologic sequelae, quality of life, fatigue, cognition) were similar after either treatment. Based on this study, various treatment guidelines now consider doxycycline as a reasonable choice for Lyme neuroborreliosis.

Lyme encephalomyelitis, involving the brain parenchyma as evidenced by focal neurologic defects or magnetic resonance imaging findings, is extremely rare, and is typically treated with two to four weeks of intravenous ceftriaxone.

**Lyme arthritis**

After treatment for Lyme arthritis with antibiotics, clinical resolution may take six to 12 months in some patients. A 30 day course of either oral doxycycline or amoxicillin led to resolution of arthritis in ~90% of 38 patients in a randomized trial, while 10-14 days of intravenous ceftriaxone led to lower success rates (19/40; 48%) in a small randomized, placebo controlled, double blind trial. Patients with Lyme arthritis typically are treated with 30 days of doxycycline, while those who continue to have symptoms of arthritis after oral antibiotics subsequently are re-treated with either doxycycline or intravenous ceftriaxone. Between 10% and 20% of patients may develop “antibiotic refractory” Lyme arthritis, a proliferative synovitis that no longer responds to antimicrobial therapy and requires therapy with intra-articular corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), hydroxychloroquine, methotrexate, biologic response modifiers, or even synovectomy.

**Acrodermatitis chronica atrophicans**

For ACA, observational studies have shown disappointing results of shorter term therapies—eg, intravenous ceftriaxone for two weeks or doxycycline for 20 days, while treatment success was 85% to 100% with doxycycline for up to four weeks. Hence, a treatment duration of four weeks is recommended. Resolution may take many months after antibiotic therapy, while skin atrophy and neuropathy often are irreversible.

**Chronic symptoms attributed to Lyme borreliosis**

Most people with Lyme borreliosis respond well to antimicrobial treatment. Despite antibiotic therapy, some patients with Lyme borreliosis develop disabling persistent symptoms, including fatigue, pain, and neurocognitive disturbances. Their exact incidence, pathogenesis, and prognosis are not well known and are an ongoing source of debate. Longlasting signs and symptoms attributed to Lyme borreliosis often are referred to as “chronic Lyme.” It is essential to discriminate antibiotic therapy failure, which results in progressive infection or persistent signs at the primary sites of infection, from new subjective symptoms developing after resolution of the initial disease manifestations. Other patients seek medical attention for longlasting symptoms which are usually medically unexplained, questioning whether these may be attributable to an unnoticed episode of Lyme borreliosis, even when there is little or no evidence of previous *B. burgdorferi* sl infection (fig 2).

**Persistent infection**

In patients with ACA, diagnosis is often delayed, and duration of signs and symptoms for many years have been reported. Even skin biopsy samples from untreated lesions present for ≥10 years reveal positive PCR and culture results, indicating an active infection that can persist for years.
After antibiotic treatment, culture results become negative, and skin lesions and accompanying signs may resolve completely, whereas local atrophy may persist in others.\(^25\,57\) Whereas a primate model has suggested that the persistence of bacteria after antibiotic therapy may drive other Lyme borreliosis manifestations,\(^135\,136\) ACA is the only manifestation of Lyme borreliosis in humans where chronic infection has been unequivocally demonstrated. Reported antimicrobial treatment failure rates, defined as development of disseminated Lyme borreliosis after treatment of early Lyme borreliosis, are low (≤1%).\(^121\,123\) In most studies where \(B\) \(burgdorferi\) sl was cultured from skin biopsy specimens of erythema migrans lesions before antibiotic therapy, post-treatment cultures yielded negative results.\(^51\,122\,137\) Recurrences of erythema migrans are not uncommon in endemic areas, and molecular typing showed that repeat episodes of erythema migrans in 17 appropriately treated patients were caused by re-infection and not relapse.\(^138\)

**Immune response**

Ongoing infection has not been shown in patients who have been treated for Lyme arthritis. However, persistent or recurrent synovial inflammation is observed in up to one third of patients after first antibiotic treatment, and in 10-17% after repeated...
courses, the latter being referred to as antibiotic refractory Lyme arthritis. In these cases, there is no clinical benefit from prolonged or recurrent antibiotic courses, but most patients do respond to immunosuppressive therapy. Hypotheses on the underlying mechanisms include persistence of non-viable spirochetal components or debris in the joint resulting in recurrent synovitis, and potential immunological mechanisms, such as auto-antibodies, autoimmune inflammatory processes, and dysregulated T cell responses. Likewise, association with HLA-DR alleles, upregulated expression of specific microRNA, and a Toll-like receptor 1 polymorphism have been suggested. Together with the observation that synovial PCR and culture results are negative or show non-viable spirochetes after antibiotic treatment, antibiotic refractory Lyme arthritis is likely based on immunological mechanisms, and persistence of Borrelia burgdorferi s.l infection as a cause is highly unlikely.

Residual damage
In patients with Lyme neuroborreliosis, longlasting signs may be attributable to irreversible neurological injury caused by the infection. Persistent symptoms have been reported by 12-48% of 77 and 85 patients in two prospective follow-up studies. Specific neurologic findings have been observed in 30% of patients included in a randomized treatment trial at four months, and 25-28% at two to five years in prospective and retrospective cohorts, including radiculopathy, paresis, hyposensibility, or hearing loss, without evidence for microbiological persistence. In a prospective case-control study including 50 patients with Lyme neuroborreliosis and matched controls, patients had a statistically significantly lower quality of life after 30 months, measured by the Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36) physical component summary. Delayed start of treatment, symptoms before treatment, and non-complete recovery after four months were possible predictors of a poorer quality of life and severe fatigue. The association of unfavorable outcomes with longer duration or severity of symptoms before the start of treatment supports the concept of irreversible neurological damage as the underlying mechanism. Similar long term neurological sequelae after microbial eradication have been observed in bacterial meningitis caused by other bacteria.

Functional disability and neurocognitive symptoms
The reported prevalence in observational studies of persistent symptoms, such as musculoskeletal pain, fatigue, and cognitive complaints varies considerably, between 0% and 48%. Case definition, Lyme borreliosis manifestation, follow-up, geographic location, and use of self-reported symptoms rather than validated measures might explain the divergence in prevalence. In a prospective study, 26/71 (36%) patients had self-reported ongoing symptoms at six months after treatment of erythema migrans. In 11%, subjective symptoms were associated with functional disability as measured with the SF-36 questionnaire, while none had microbiological or clinical evidence for ongoing infection. Another prospective study among 128 US patients with culture confirmed erythema migrans followed for >10 years found a 10.9% incidence of self-reported ongoing symptoms, predominantly memory or concentration difficulties, fatigue, and joint pain. In most patients, one or more symptoms persisted for >10 years.

The appreciation of long term outcomes of Lyme borreliosis is hampered by the lack of proper control groups in most studies. In a controlled prospective study from Europe in 285 patients with erythema migrans, the prevalence of symptoms was highest at baseline (33.3%), decreasing to 4.6% at six months and 2.2% at 12 months. In 259 matched controls without Lyme borreliosis, these rates were similar (3.0% at 12 months). Microbiological failure requiring retreatment was documented in two cases only. This particular study did not include patients with multiple erythema migrans or manifestations such as Lyme neuroborreliosis, who might have a greater likelihood of developing persistent symptoms. Also, Borrelia burgdorferi ss infected patients in the US are more likely to be symptomatic at baseline, and therefore might have a greater likelihood of developing persistent symptoms. While many patients report cognitive problems such as memory loss, word-finding difficulties, and lack of concentration, subjective memory complaints were not associated with impaired objective test performances in a prospective study on 279 patients with persistent symptoms attributed to Lyme borreliosis. Only 3% of patients included in that study were classified as having clinically impaired cognitive performance compared with normative data.

It has been hypothesized that chronic pain and fatigue syndromes may be part of a central sensitization syndrome that follows non-infectious or infectious diseases. Central sensitization is thought to involve activation of central neurons, leading to synaptic and neurotransmitter changes, and an increased sensitization to pain signals that may last for months or years. After Lyme borreliosis, such a mechanism might be elicited by past infection, persistence of remnant bacterial proinflammatory triggers, or other physiological or behavioral mechanisms.
Lyme borreliosis meeting the CDC surveillance criteria. Additional criteria exclude patients with untreated Lyme borreliosis or other tickborne infections, and those with objective persistent signs of the initial episode of Lyme borreliosis, such as recurrent arthritis, ACA, or neurologic sequelae of Lyme meningoradiculitis. Others have proposed to better define the “functional impact” component of the case definition, using an SF-36 questionnaire threshold. By definition, patients with PTLDs have no compelling clinical or laboratory support for the diagnosis of ongoing B burgdorferi sl infection, and neither have they signs suggesting immunological phenomena, such as recurrent synovitis, or irreversible nerve damage after Lyme neuroborreliosis. Several hypotheses on the causes of PTLDs exist. First, microbiological mechanisms have been considered, including tickborne co-infections. Whereas ticks that transmit B burgdorferi sl are known vectors of other human pathogens, none of these pathogens are known to cause chronic infections. Whereas ticks that transmit B burgdorferi sl have been reported in human tissue specimens in a small number of cases, none of the patients had symptoms resembling those of PTLDs, and conversely, morphologic variants have never been identified in patients with chronic Lyme attributed symptoms. Second, immunogenetic mechanisms have been proposed, but prospective observational studies on dysregulated immune responses and case-control studies on autoimmune processes have been inconclusive. Third, associations of PTLDs have been described with demographic, clinical, and epidemiological patient characteristics, such as advanced age, female sex, comorbidity, and duration of pre-treatment symptoms. Finally, cognitive behavioral characteristics, including depression, anxiety, negative affect, and catastrophizing have been associated with the risk of developing persistent symptoms.

Trials of prolonged antimicrobial therapy
Empirical antibiotic treatment studies have targeted the possibility of concealed infection in patients with persistent symptoms, despite the weight of evidence against persistent infection as the explanation for PTLDs. Initial open cohort studies have claimed successful antimicrobial therapy in patients with “chronic Lyme.” Oral tetracycline for a median of four months was reportedly associated with a 90% success rate in a case series of 277 patients. Likewise, the combination of clarithromycin and hydroxychloroquine reportedly was as effective as prolonged tetracycline in another series of 235 cases. Most patients improved within two weeks after initiation of therapy, and all patients had improved after three months. However, in both studies, inclusion criteria were not clearly defined, and serologic reactivity against B burgdorferi sl, but no documented Lyme borreliosis, was required. The studies were non-randomized and uncontrolled, and did not use standardized questionnaire outcomes.

Five randomized controlled clinical trials have been performed in patients with persistent symptoms attributed to Lyme borreliosis (table 2). One trial did not find any beneficial effects on quality of life in 115 patients randomized to prolonged therapy compared with the matching placebo group. While the study found improvement in self-reported cognitive functioning in both randomization arms, no improvement in objective neurocognitive functioning was found.

In a small study, 37 patients with memory impairment were randomized to ceftriaxone versus placebo. At 12 weeks, the ceftriaxone group showed a statistically significantly greater effect on objective neurocognitive functioning, but this was not sustained to week 24, whereas the effect on self-reported fatigue and physical functioning was only sustained among a subgroup more severely affected at baseline. How this short term cognitive improvement relates to other patients with PTLDs is uncertain, as participants were selected from a cohort of >3000 patients, and were required to have objective cognitive impairment on neuropsychological testing, which is rare among patients with PTLDs.

Another trial randomized 55 patients with severe fatigue to four weeks of ceftriaxone versus placebo. The primary endpoint failed to show improvement in neuropsychological performance, but self-reported fatigue improved in the group taking ceftriaxone. Despite the statistically significant effect reported, the authors themselves conclude that the study does not support the use of additional antibiotic therapy, because fatigue, a non-specific symptom, was the only outcome that improved.

A trial that randomized 86 patients with “a recurrence of Lyme borreliosis symptoms” to oral amoxicillin for three months or placebo was hampered by several shortcomings. It was prematurely terminated because of slow recruitment, the publication did not provide details on the intention-to-treat population, and a large proportion of patients were excluded from the analysis “because of persistent symptoms.”

In another trial, the PLEASE trial, 281 patients were randomized to receive 14 days of ceftriaxone, followed by 12 weeks of either doxycycline, clarithromycin plus hydroxychloroquine, or placebo. Neither regimen of 12 weeks of therapy yielded benefit over placebo with respect to serial mental and physical health related quality of life measures during follow-up until 52 months. This study has built upon lessons learnt from earlier studies. Choice and duration of the treatment regimens were based on uncontrolled studies which reported that almost 75% of patients improved within one month and 92% to 100% within three months of treatment, which suggested that a three month regimen should be optimal to assess whether those observations are sustained when placebo controlled. Whereas...
While prolonged antimicrobial treatment is not affect the outcomes. Second, all three study groups patients without prior oral pretreatment did not compare longer term with standardized shorter term designed as a randomized, placebo controlled trial to antibiotic pretreatments. Consequently, the study was while previous trials allowed for a wide variance of phase, to standardize and synchronize pretreatment, label antibiotics preceding the randomized treatment debate. First, patients received two weeks of open aspects of the study design have been subject of prospectively assessed in a pilot study. Three summary score specific for patients with PTLDS, clinically relevant treatment effect on the SF-36 life. Finally, the endpoint was based on a minimal was corrected for baseline health related quality of earlier randomized trials might have been influenced by baseline differences, the PLEASE trial analysis was corrected for baseline health related quality of life. Finally, the endpoint was based on a minimal clinically relevant treatment effect on the SF-36 summary score specific for patients with PTLDS, as prospectively assessed in a pilot study. Three aspects of the study design have been subject of debate. First, patients received two weeks of open label antibiotics preceding the randomized treatment phase, to standardize and synchronize pretreatment, while previous trials allowed for a wide variance of antibiotic pretreatments. Consequently, the study was designed as a randomized, placebo controlled trial to compare longer term with standardized shorter term therapy. Sensitivity analyses showed that excluding patients without prior oral pretreatment did not affect the outcomes. Second, all three study groups slightly improved during the 52 weeks of follow-up, irrespective of randomization arm, and some have attributed this to the standardized pretreatment with ceftriaxone, rather than placebo effects or regression to the mean. However, regression of symptoms, including fatigue severity, has consistently been reported in the placebo arm of other studies, and was of similar magnitude (table 2). This is in agreement with the finding that positive pretreatment expectancies and higher self-efficacy were the major predictors of outcome, regardless of randomization arm. Third, it has been argued by some that 14 weeks of treatment was insufficient to show a beneficial effect on alleviation of symptoms, in contrast to the earlier uncontrolled studies. While prolonged antimicrobial treatment is not uncommon for various infectious diseases, such as tuberculosis, in the case of TB it is aimed at preventing microbiological relapse, and not at a delayed onset of clinical alleviation, as no infectious diseases have been described in which the initial effect on signs, symptoms, and laboratory findings is delayed beyond the first three months of effective therapy.

In summary, five randomized clinical trials have provided little support for prolonged antibiotic treatment in patients with persistent symptoms attributed to Lyme borreliosis. While smaller studies reported limited, or non-sustained effects on selected outcomes, the two largest trials did not find beneficial effects of prolonged treatment on any of the domains studied (table 2). Management of patients with persistent Lyme attributed symptoms Attributing a cause to medically unexplained symptoms is challenging, and the lack of abnormal test results or objective findings can be frustrating for both patients and physicians. A stepwise approach can help assess whether persistent symptoms attributed to Lyme borreliosis are indeed related to previous B burgdorferi sl infection, and may be caused by active infection (thus, potentially amenable to antimicrobial treatment), or caused by immune mediated mechanisms or residual damage (fig 3, box 3). A temporal relation of persistent constitutional symptoms with primary Lyme borreliosis may suggest PTLDS (box 2). For a large group of patients who have little or no evidence of previous B burgdorferi sl infection, who understandably seek explanation for chronic fatigue, pain, and other incapacitating

**Study design**  Randomized, placebo controlled, double blind trial

**Inclusion criteria**

- Adults with physician documented Lyme borreliosis. Persistent symptoms that had begun <6 months after initial infection and persisted for >6 months.
- Adults with physician documented Lyme borreliosis, with serologic confirmation. Persistent symptoms that had begun coincident with initial infection.
- Adults with physician documented Lyme borreliosis, with serologic confirmation, current positive IgG western blot, and subjective and objective memory impairment (Wechsler Memory Scale-III).

**Pre-treatment**

- ≥1 course of recommended antibiotic regimen
- ≥3 weeks of doxycycline or intravenous ceftriaxone

**Randomization**

- 1:1
- 1:1

**Intervention arm**

- Intravenous ceftriaxone 2 g once daily for 30 days followed by oral doxycycline 100 mg twice daily for 60 days
- Intravenous ceftriaxone 2 g once daily for 28 days
- Intravenous ceftriaxone 2 g once daily for 70 days
- Oral amoxicillin 3 g once daily for 90 days
- Oral amoxicillin 3 g once daily for 28 days
- Oral amoxicillin 3 g once daily for 56 days
- Intravenous placebo for 70 days
- Intravenous placebo for 56 days

**Control arm**

- Intravenous placebo for 30 days followed by oral placebo twice daily for 60 days
- Intravenous placebo for 28 days
- Intravenous placebo for 70 days
- Oral placebo for 90 days
- Oral placebo for 56 days

**Follow-up**

- 180 days
- 6 months
- 24 weeks
- 6 months
- 1 year

**Primary endpoint**

- SF-36 score at 180 days
- Fatigue (FSS-11 score) and mental speed (α-arithmetic test) at 6 months
- Neurocognitive performance (6 domains tested) at 12 weeks
- SF-36 score at 6 month
- SF-36 score (PCS) at 14 weeks

**Number of subjects (ITT analysis)**

- 115
- 55
- 37
- 86
- 280

**Primary outcome (intervention group/placebo group)**

- SF-36 (total score): improved in 37% vs 40%, Δ −3%, 95% confidence interval −26 to 20 (ns)
- Fatigue assessed by FSS-11 improved in 64% vs 19%, ratio 3.5, 95% confidence interval 1.50 to 8.03; P=0.001
- Mental speed (α-A test) improved in 8% vs 9% (ns)
- Neurocognitive performance (longitudinal mixed effects model) drug vs placebo at week 12, 0.28; 95% confidence interval −0.01 to 0.56; P=0.053 at week 24, 0.04; 95% confidence interval −0.24 to 0.33; P=0.76
- SF-36 (total score): improved in 46% vs 18% (P=0.007)
- Mean PCS score at 12 weeks, 40.4 v 36.0; MCS, 4.3 v 5.1; 6 (ns)
- Mean PCS at 24 weeks 42.0 v 36.8;
- MCS, 42.1 v 50.7 (ns)
- Average improvement in 48 evaluable patients, PCS, 8.5 v 7 (ns)
- Mean PCS at 14 weeks, 40.2 v 40.5 v 40.1 (ns)

**Secondary outcomes (intervention group/placebo group)**

- PCS improved in 35% vs 26%, Δ 9%; 95% confidence interval −8.26 to 20 (ns)
- MCS improved in 33% vs 38%, Δ −5%, 95% confidence interval −2.2 to 13 (ns)
- Fatigue assessed by VAS at primary endpoint, improved in 29% vs 10% (ns).
- No significant difference in pain, mood, and perceived health changes between groups.
- CSF OspA antigen status positive to negative, 4/4 v 3/4 (ns)
- Mean PCS score at 12 weeks, 40.4 v 36.0;
- MCS, 4.3 v 5.1; 6 (ns)
- Mean PCS at 24 weeks 42.0 v 36.8;
- MCS, 42.1 v 50.7 (ns)
- Average improvement in 48 evaluable patients, PCS, 8.5 v 7 (ns)
- Average improvement in 48 evaluable patients, PCS, 8.5 v 7 (ns)
- Mean MCS at 14 weeks, 40.2 v 40.5 v 40.1 (ns)
- PCS at 26, 40, and 52 weeks, no significant difference between treatment arms.
- Neurocognitive performance (5 domains tested) at 26, 40, and 52 weeks, no significant difference between treatment arms.

Table 2 | Overview of randomized controlled treatment trials in patients with symptoms attributed to previously documented Lyme borreliosis

(continued)
mean decrease in fatigue score, 14%; mean increase in PCS, 7 points; MCS, 6.2 points

Table 2: Continued

<table>
<thead>
<tr>
<th>Study</th>
<th>Positive</th>
<th>Placebo</th>
<th>CI</th>
<th>Significance</th>
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<tbody>
<tr>
<td>Klampfer, 2001</td>
<td>26% of patients improved &gt;0.7 points on FSS-11 fatigue scale at 6 months</td>
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<tr>
<td>Kusnir, 2003</td>
<td>No significant effect of primary endpoint</td>
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<tr>
<td>Fallon, 2008</td>
<td>23% of patients improved &gt;6.5 points on PCS; 38% of patients improved &gt;7.9 points on MCS</td>
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<tr>
<td>Cameron, 2008</td>
<td>Inclusion criteria for prior Lyme borreliosis and current symptoms not specified. 38 of 86 patients were excluded from the primary analysis due to baseline levels of impairment. No significant difference between groups in PCS score at primary endpoint</td>
<td></td>
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</tr>
<tr>
<td>Berende, 2016</td>
<td>26% of patients improved &gt;6.5 points on PCS; 38% of patients improved &gt;7.9 points on MCS</td>
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</tr>
</tbody>
</table>

Table 2: Continued

Co-infections

Other microorganisms present in ticks

Numerous bacteria, parasites, and viruses have been detected in *Ixodes* ticks. Bacterial pathogens include: *Borrelia burgdorferi*, which is the causative agent of Lyme borreliosis; *Anaplasma phagocytophilum*, which causes anaplasmosis; and *Ehrlichia chaffeensis*, which causes ehrlichiosis. Parasitic infections include *Babesia microti*, which causes babesiosis, and *Babesia miyamotoi*, which causes babesiosis. Viral infections include *Barréria mayonii*, which causes Barréria mayonii fever, and *Barréria miyamotoi*, which causes Barréria miyamotoi fever. In addition, *Borrelia mayonii* has been detected in ticks in Europe, the US, and Asia; for example, *Ehrlichia muris* in Europe, *Anaplasma phagocytophilum* in the US, and *Ehrlichia chaffeensis* in Asia. Notably, the mere presence of a microbe—let alone its DNA—does not necessarily lead to disease.

Lyme borreliosis: evidence for role of co-infections

Co-infection of *Ixodes* ticks with multiple tickborne pathogens is well established. Although even in regions where multiple tickborne diseases are endemic, human co-infections appear to be relatively rare. In the US, *B. burgdorferi* ss-*Anaplasma phagocytophilum* and *B. burgdorferi* ss-*Babesia microti* co-infections are relatively common. Experimental evidence suggests that *Anaplasma phagocytophilum* and *Borrelia burgdorferi* ss-*Babesia microti* co-infections can alter the clinical presentation of Lyme borreliosis and may contribute to persistent disease. In addition, co-infections may lead to more severe symptoms and a higher risk of relapse. Therefore, it is important to consider the possibility of co-infections when treating patients with Lyme borreliosis or when monitoring the course of disease.

Clinicians caring for patients with Lyme borreliosis should be aware of the potential role of co-infections in the pathogenesis of the disease. This awareness is crucial for the development of effective treatment strategies and for the management of patients with persistent disease. In close consultation with the patient, the optimal management strategy should be determined, without reverting to unsubstantiated, irrational, or even potentially harmful therapies.
may alter the course of acute Lyme borreliosis but clinical data are inconclusive. In contrast, human co-infection with *Babesia microti* can increase the duration and severity of symptoms caused by acute Lyme borreliosis. Of note, patients with acute Lyme borreliosis accompanied by persisting high grade fever in the US, any fever in Europe, or abnormal blood counts (anemia, thrombocytopenia, or leukopenia) should raise a suspicion of co-infection.

In contrast, there is little evidence for the notion that “chronic Lyme” can be attributed to Lyme borreliosis and a wide range of co-infections. These include the pathogens mentioned above, but also other microorganisms, such as *Chlamydia*, *Brucella*, or *Mycoplasma* species, *Toxoplasma gondii*, Epstein-Barr virus, cytomegalovirus, or human herpes virus-6. However, these patients frequently lack clinical symptoms compatible with such infections. A systematic review of patients diagnosed with “chronic Lyme” did not find evidence for chronic anaplasmosis or babesiosis in humans, tick transmission of *Bartonella* species, or *B. burgdorferi* sl-Bartonella co-infections. In Europe, a large prospective clinical study is currently ongoing, assessing the role of several known *Ixodes Ricinus*-borne pathogens in the development of longlasting symptoms.

**Post-exposure prophylaxis**

A meta-analysis of four placebo controlled clinical trials (totaling 1082 patients) in the US showed a
risk of developing Lyme borreliosis of 2.2% (95% confidence interval 1.2% to 3.9%) in the placebo group, compared with 0.2% (95% confidence interval 0.0% to 1.0%) in the prophylaxis group,13 indicating that prophylaxis to ~50 individuals prevents one case of Lyme borreliosis.208 A trial with topical azithromycin was stopped prematurely because of a lack of effect.203 In current guidelines from the US and Europe, watchful waiting is primarily recommended, while a single dose of doxycycline (200 mg) within 72 hours after a tick bite206 may be offered in highly endemic settings, when the tick has been attached for longer periods.157 206 207

**Vaccination**

**The OspA vaccine**

In the late 1990s, two vaccines, LYMErix208 and ImuLyme,204 were assessed in large phase III clinical, double blind, randomized, placebo controlled trials. Both vaccines were based on recombinant OspA of *B burgdorferi* ss. The vaccines were well tolerated, efficacy ranged from 76% to 92% after three immunizations, and they were shown to be cost effective.208-211 LYMErix was commercially launched in the US in 1998, and in 2002, manufacturer GSK voluntarily withdrew the vaccine, citing poor sales on lack of demand.212 However, the reasons were multifactorial and extensively discussed previously,213 214 cumulating in class action lawsuits and final withdrawal of the vaccine. Several OspA based veterinary vaccines are still available,215 but a commercial vaccine to prevent Lyme borreliosis in humans does not exist.

**Modified OspA vaccines**

As multiple *B burgdorferi* ss genospecies can cause Lyme borreliosis, second generation OspA vaccines targeting multiple *B burgdorferi* ss serotypes are being developed. Baxter BioScience has developed a chimeric recombinant vaccine that contained six OspA serotypes,216 lacking the alleged “auto-reactive” *B burgdorferi* ss epitope. Phase I/II vaccine trials have shown safety and immunogenicity in naive and previously *B burgdorferi* ss exposed individuals.217 218 Another novel multivalent OspA vaccine, VLA15, consists of three heterodimers linking C-termini of two OspA serotypes and covering six clinically relevant *B burgdorferi* ss serotypes,219 while the alleged “auto-reactive” epitope was replaced with the corresponding sequence of *B afzelii*. A phase I trial indicated seroconversion of 71.4% to 96.4% for multiple OspA serotypes after three doses of VLA15, which were well tolerated.220 VLA15 is currently assessed in phase II clinical trials with higher dosages and alternative vaccination schedules (NCT03769194/NCT03970733).

**New vaccination horizons**

Other spirochetal recombinant protein based vaccines, including a vaccine that targets a *B burgdorferi* ss protein of unknown function, BB0405,221 and novel delivery strategies are under development.222 223 Alternatively, vaccination against tick proteins is considered,224 based on the phenomenon known as “tick immunity”: guinea pigs, rabbits, and possibly humans, develop immune responses against tick proteins after repeated tick infestation, resulting in impaired tick feeding and protection against *B burgdorferi* ss infection.223 Regardless of the approach, a future human vaccine would need to be sufficiently safe, efficacious, and cost effective, to achieve acceptance from the medical community and public and to prevent a repetition of the past.225 226

**Guidelines**

Guidelines on management of Lyme borreliosis are available in the US 157 225 226 and Europe.66 206 207 227 228 For the antibiotic treatment of Lyme borreliosis, the recommended agents, doses, and durations are highly consistent through different guidelines, and are predominantly based on studies described in table 3. Alternative recommendations, provided in a position paper by the International Lyme and Associated Diseases Society (ILADS), have not provided any credible clinical or scientific evidence.

**Box 3: Stepwise approach to management of patients with persisting symptoms attributed to Lyme borreliosis**

- **Goal:** to assess whether persisting symptoms are related to previous *B burgdorferi* infection, and may be due to active infection and, thus, potentially amenable to antimicrobial treatment
- **A careful medical history should show whether there may have been a *B burgdorferi* infection and clinical signs of localized or disseminated Lyme borreliosis**
- **Physical examination should focus on persistent signs at the primary sites of infection or new, localized signs of disseminated infection that may indicate persistent infection. If persisting infection is deemed unlikely, immune mediated arthritis or neuroborreliosis induced residual damage should be ruled out**
- **A temporal relation of subjective symptoms and primary Lyme borreliosis may suggest PTLDS**
- **Consider other underlying diseases or conditions that may explain the patient’s symptoms, or laboratory or imaging abnormalities that might suggest an undiagnosed process**
- **In patients with constitutional symptoms and little or no evidence of previous *B burgdorferi* infection, the evidence is against persistent *B burgdorferi* infection as the explanation for persistent symptoms, and treatment trials have provided evidence against prolonged antibiotic therapy**
- **Listen to the patient’s concerns and acknowledge their suffering, and discuss the pitfalls and misconceptions surrounding the diagnosis and management of Lyme borreliosis**

**Table 3. Alternative recommendations, provided in a position paper by the International Lyme and Associated Diseases Society (ILADS)**
to support prolonged antibiotic therapy. Their designation as "evidence based guidelines" belies their anecdotal nature and lack of coherent and evidence-based guidance. 226

**Conclusion**

The manifestations of Lyme borreliosis are diverse, the diagnosis is not always straightforward, diagnostic tests may have limitations, and their results should be interpreted in the context of the clinical symptoms. However, the disease generally responds well to antibiotic treatment. Despite antibiotic therapy, patients may develop disabling persistent symptoms, sometimes referred to as "chronic Lyme." For proper patient management, it is of critical importance to discriminate antibiotic therapy failure from immune-driven post-infectious phenomena such as relapsing Lyme arthritis, residual tissue damage, such as post-neuroborreliosis neuropathy, or new subjective symptoms developing after resolution of the initial disease manifestations. The latter may be classified as PTLDS, of which the pathogenesis has not fully been elucidated. 134 Finally, "chronic Lyme" remains a popular consideration for patients, often with little or no evidence of previous *B. burgdorferi* infection, who understandably seek explanation for fatigue, pain, and other incapacitating symptoms. These patients, who are indisputably suffering regardless of the cause of their symptoms, deserve a thorough analysis whether there may have been an undiagnosed *B. burgdorferi* infection, or other post-infectious sequelae. Often, the lack of objective findings and abnormal test results are frustrating for physicians as well as for patients. Good medical care for these patients includes listening, understanding, and discussing personalized treatment options, including non-pharmacological options such as rehabilitation. Future research may reveal additional

### Table 3 | Overview of treatment guidelines for Lyme borreliosis*

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Recommendations</th>
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<tr>
<td><strong>Prophylaxis</strong></td>
<td>• Not addressed in all guidelines&lt;br&gt;• Routine use of antibiotic prophylaxis is not recommended in two guidelines 157 227&lt;br&gt;• Specific conditions in which a single dose of doxycycline (200 mg for adults if not contraindicated) may be offered are considered by IDSA: bite by tick species known to potentially transmit <em>B. burgdorferi</em> with a local infection rate of ≥20%, tick-attached for ≥36 hours (estimated), and start of prophylaxis within 72 hours after removal of the tick 157&lt;br&gt;• ILADS recommends treatment with doxycycline for 20 days in all patients with evidence of tick feeding 226</td>
</tr>
<tr>
<td><strong>Erythema migrans</strong></td>
<td>• Oral doxycycline therapy for 10–21 days as first line therapy 157 206 207 227 228&lt;br&gt;• Second line includes oral amoxicillin (mostly preferred), cefuroxime axetil, or phenoxymethylpenicillin for 14–21 days 157 206 207 227 228&lt;br&gt;• Azithromycin (or other macrolides) for 5–17 days as third line option 157 207 227&lt;br&gt;• Longer duration in case of concomitant non-focal symptoms or multiple erythema migrans is specifically not recommended in some guidelines, 206 207 whereas in others it is recommended 227&lt;br&gt;• ILADS recommends oral antibiotics for 4–6 weeks (amoxicillin, cefuroxime, or doxycycline) or 21 days for azithromycin, with continuation of therapy if full recovery has not been achieved 227</td>
</tr>
<tr>
<td><strong>Lyme neuroborreliosis</strong></td>
<td>• Intravenous ceftriaxone for 10–28 days favored for meningitis/radiculopathy by several guidelines 157 207 227 228 with oral doxycycline as reasonable alternative Other guidelines favor doxycycline as first choice 226 or consider both equivalent 228 For cranial neuritis, doxycycline is generally favored</td>
</tr>
<tr>
<td><strong>Lyme arthritis</strong></td>
<td>• Doxycycline for 28–30 days as first line treatment, 206 207 227 in absence of neurologic disease 157&lt;br&gt;• If no improvement after first line therapy: intravenous ceftriaxone for 28 days 157 206&lt;br&gt;• National Institute for Health and Care Excellence (NICE) guidelines recommend oral amoxicillin for 28 days as first alternative to doxycycline, and intravenous ceftriaxone as second alternative 227&lt;br&gt;• If persistent after repeated antibiotic regimens, reactive/inflammatory arthritis is considered and anti-inflammatory therapy may be offered 157 206</td>
</tr>
<tr>
<td><strong>ACA</strong></td>
<td>• Doxycycline for 28–30 days as first line treatment, 206 207 227 whereas shorter duration of oral treatment (14–21 days) is recommended in two guidelines 157 228&lt;br&gt;• Intravenous ceftriaxone for 28 days as second line 228 or third line 207 or in case of concomitant neurological symptoms as first choice for 14–21 days 227&lt;br&gt;• Irreversible skin damage (skin atrophy, sensory deficits) may persist 157 206 227</td>
</tr>
<tr>
<td><strong>Borrelial lymphocytoma</strong></td>
<td>• Therapy similar to that of erythema migrans, but for a minimal duration of 14–21 days 157 228 to 21 days 206 227&lt;br&gt;• NICE guidelines withhold from general recommendations because of its low incidence and lack of evidence 207</td>
</tr>
<tr>
<td><strong>Lyme carditis</strong></td>
<td>• Oral doxycycline (or equivalent) for 14–30 days 157 206 207 228&lt;br&gt;• Intravenous ceftriaxone in case of symptomatic carditis, 207 switch to oral antibiotics based on clinical response, for a total duration of 14–21 days 157 206</td>
</tr>
<tr>
<td><strong>Ongoing symptoms after treatment for Lyme borreliosis</strong></td>
<td>• If there is no suspicion of re-infection or failure of antibiotic therapy after careful review of a patient’s history and symptoms 206 207 and in patients with PTLDS, 157 227 prolonged antibiotic treatment or re-treatment is not recommended&lt;br&gt;• ILADS guidelines suggest antibiotic treatment may be considered in the heterogeneous population of “patients with persistent manifestations of Lyme disease” for a duration of 4–6 weeks or longer, as “the evidence regarding persistent infection is at hand and the potential benefits of retreatment are adequate to support those who wish to treat, but is not overwhelming enough to mandate treatment.” For patients who partially respond after 4–6 weeks, “the decision to continue treatment may depend on the length of time between the initial and subsequent re-treatment, the severity of the patient’s response to retreatment, the severity of the patient’s current impairments”226 206 207 227 228</td>
</tr>
</tbody>
</table>

*Two guidelines specifically focus on neuropathic Lyme borreliosis manifestations, 225 226 one on dermatologic manifestations, 157 and one on antibiotic prophylaxis after tick bite, erythema migrans, and persistent symptoms. 226

Treatment recommendations for children are largely similar to adults, although for children aged under 8 or 9 doxycycline is relatively contraindicated 157 206 207 227 228
underlying causal mechanisms, indicating how to best diagnose and treat these patients.
Contributors: HDV and FvdS performed the primary literature review for this manuscript. BJK wrote the sections on therapy, trials of prolonged therapy, and management of patients with persistent Lyme attributed symptoms. JWH wrote the sections on incidence and epidemiology, co-infections, prevention, and vaccination. FvdS wrote the section on clinical manifestations. FvdS and JWH wrote the section on laboratory support. HDV wrote the sections on chronic symptoms attributed to Lyme borreliosis and guidelines. BJK guided the writing of the full manuscript and assumed primary responsibility. All authors reviewed all sections of the manuscript, providing suggestions for included content and references, and approved the published version.

Competing interests We have read and understood the BMJ policy on declaration of interests and declare the following interests: none.

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RESEARCH QUESTIONS

• What are the main factors responsible for the rise in the abundance of *Ixodes* ticks that vector the causative agents of Lyme borreliosis; can we find effective and interdisciplinary countermeasures to halt this upsurge?

• Can we discover and develop novel diagnostics markers or tests with increased sensitivity for localized disease and early disseminated Lyme borreliosis, and tests that can differentiate between an active *B burgdorferi* s.l infection and past infection, in particular for patients with unexplained signs and symptoms after completing antibiotic treatment?

• What are effective strategies for the prevention of antibiotic refractory Lyme arthritis, and can we develop evidence based guidelines for its treatment?

• What are the underlying causal mechanisms in patients with longlasting symptoms after antibiotic treatment for Lyme borreliosis? Can we identify microbiological determinants, co-infections, immunological or genetic mechanisms, epidemiological determinants, or cognitive behavioral factors that are associated with developing persistent post-treatment symptoms?

• What is the long term outcome in patients with PTLDS? Which factors may influence their prognosis, and can we define optimal treatment strategies for these patients?

• Can we find a safe, efficacious, and cost effective vaccine that is able to protect both children and adults against Lyme borreliosis in Europe and in North America? What is needed for the general public to accept such a vaccine?

PATIENT INVOLVEMENT

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