Lyme borreliosis and other tick-borne diseases. Guidelines from the French scientific societies (II). Biological diagnosis, treatment, persistent symptoms after documented or suspected Lyme borreliosis

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Borréliose de Lyme et autres maladies vectorielles à tiques. Recommandations des sociétés savantes françaises. Argumentaire 2 : diagnostic biologique, traitement, symptômes persistants au décours d'une borréliose de Lyme documentée ou suspectée.

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Résumé

Le sérodiagnostic de borréliose de Lyme repose sur deux temps : un premier test de dépistage immuno-enzymatique (technique ELISA), puis en cas de positivité, une confirmation par immuno-empreinte (western blot), de meilleure spécificité. Dans l'érythème migrant, la sérologie ne doit pas être demandée (faible sensibilité : 30-40 %). La séroconversion se fait en 6 semaines, avec apparition des IgG (sensibilité et spécificité > 90 %). Le suivi sérologique n'est pas recommandé et le succès thérapeutique est évalué sur l'évolution clinique. Pour les formes neurologiques, il est recommandé de faire simultanément une recherche d'anticorps dans le sang et le liquide cérébrospinal (ELISA) avec recherche de synthèse intrathécale. Compte tenu de la continuité entre les formes localisées et disséminées précoces et de l'efficacité de la doxycycline en cas de neuroborréliose, elle est privilégiée en première intention pour le traitement de l'érythème migrant (durée 14 jours ; alternative : amoxicilline) et des neuroborrélioses (durée 14 jours si précoce et 21 jours si tardive ; alternative : ceftriaxone). Le traitement des formes articulaires repose sur la doxycycline, la ceftriaxone ou l'amoxicilline pendant 28 jours. En cas de symptômes persistants après une borréliose de Lyme bien traitée, il est recommandé de ne pas répéter ou prolonger l'antibiothérapie. Certains patients présentent des symptômes persistants et polymorphes après une borréliose de Lyme documentée ou supposée. Un autre diagnostic est porté chez 80 % d'entre eux.

Mots clés : borréliose de Lyme ; western blot ; neuroborréliose ; érythème migrant ; symptomatologie somatique persistante

Abstract

The serodiagnosis of Lyme borreliosis is based on a two-tier strategy: a screening test using an immunoenzymatic technique (ELISA), followed if positive by a confirmatory test with a western blot technique for its better specificity. Lyme serology has poor sensitivity (30-40%) for erythema migrans and should not be performed. The seroconversion occurs after approximately 6 weeks, with IgG detection (sensitivity and specificity both >90%). Serological follow-up is not recommended as therapeutic success is defined by clinical criteria only. For neuroborreliosis, it is recommended to simultaneously perform ELISA tests in samples of blood and cerebrospinal fluid to test for intrathecal synthesis of Lyme antibodies. Given the continuum between early localized and disseminated borreliosis, and the efficacy of doxycycline for the treatment of neuroborreliosis, doxycycline is preferred as the first-line regimen of erythema migrans (duration, 14 days; alternative: amoxicillin) and neuroborreliosis (duration, 14 days if early, 21 days if late; alternative: ceftriaxone). Treatment of articular manifestations of Lyme borreliosis is based on doxycycline, ceftriaxone, or amoxicillin for 28 days. Patients with persistent symptoms after appropriate treatment of Lyme borreliosis should not be prescribed repeated or prolonged antibacterial treatment. Some patients present with persistent and pleomorphic symptoms after documented or suspected Lyme borreliosis. Another condition is eventually diagnosed in 80% of them.

Keywords: Lyme borreliosis; western blot; neuroborreliosis; erythema migrans; persistent somatic symptoms

1. Diagnostic tests for Lyme borreliosis

The performance of diagnostic tests depends on the clinical presentation of the disease (Tables 1 and 2).

1.1 Serological tests

All national, European, or American evidence-based guidelines recommend the two-tier serology for the serodiagnosis of Lyme borreliosis. The two-tier serology is first based on an immunoenzymatic technique (ELISA) and then, if positive or equivocal, on a confirmatory immunoblot test (western blot, WB) with increased specificity [1]. No screening test is available for active *Borrelia* infection as asymptomatic seropositivity is highly common [2]: seropositivity alone is not enough to establish the diagnosis of Lyme borreliosis.

Almost all currently available ELISA tests include antigens from the three main European species pathogenic to humans (*Borrelia afzelii, Borrelia garinii,* and *Borrelia burgdorferi* sensu stricto), with better sensitivity and specificity than first-generation ELISA tests. ELISA tests should be used as first-line tests. Several studies demonstrated that one-tier (ELISA test alone) and two-tier strategies (ELISA +/- WB) had similar performances. No study has ever demonstrated the superiority of ELISA test alone versus the two-tier strategy (ELISA +/- WB) (***grade B***) [3, 4]. Comparison studies of characteristics and performance of commercialized serological tests – with details of the antigens used, the study population, and the disease stages – are available from the websites of the French Agency for the Safety of Health Products (French acronym ANSM, *Agence nationale de sécurité du médicament et des produits de santé*) and of the national reference center for *Borrelia* (French acronym CNR, *Centre National de Référence*). These studies should be used as a guiding tool for biologists and as reference documents to standardize the use of these tests and to maximize diagnostic performances. The use of serological techniques in laboratories for biomedical analysis complies with the ISO 15189 standards and is assessed by repeated audits for accreditation purposes.

During early localized manifestations of Lyme borreliosis (erythema migrans), Lyme serology has poor sensitivity (30-40%). Diagnosis at this localized stage of the disease should therefore not be based on serological testing. Seroconversion occurs within six weeks approximately, with IgG detection. Six weeks after clinical symptom onset, the serological test is associated with >90% sensitivity and specificity [3-5]. For early disseminated manifestations

with symptom onset within six weeks after the tick bite (e.g., early Lyme neuroborreliosis), the blood serological test may be negative and the biological diagnosis should be based on the results of the cerebrospinal fluid (CSF) analysis. The sole persistence of IgM beyond six weeks should be considered a false positive result, because of the high risk of non-specific cross-reactions [6-8].

The sensitivity of serological tests in late disseminated neurological, cutaneous, or joint manifestations is close to 100%, and very high IgG levels are common [3, 9]. Immunoblot testing always reveals IgG targeted against numerous *Borrelia burgdorferi* sensu lato antigens. The ELISA serological test is rarely negative in patients presenting with late Lyme borreliosis: two cases of acrodermatitis chronica atrophicans (ACA) with an atypical clinical presentation, one case of Lyme arthritis, and one case of seronegative late Lyme neuroborreliosis have been reported [10-12]. Thus, a negative Lyme serological test result at this late stage of the disease should lead to questioning the diagnostic hypothesis ***(grade B)***.

The sole presence of IgG, without IgM, is common in late manifestations of Lyme borreliosis, even if the culture is positive (i.e., 15-20% of ACA cases). High levels of antibodies can be observed in treated patients several years after recovery. The treatment should in that case not be resumed [13-15]. Serological follow-up is therefore not recommended, and treatment success should be assessed based on clinical signs and symptoms ***(grade A)***.

Neurological manifestations should lead to simultaneous quantification of specific anti-*Borrelia burgdorferi* sensu lato IgG and total IgG in the blood and in the CSF (ELISA test), to calculate intrathecal synthesis index [1, 16] ***(grade B)***.

The presence of anti-*Borrelia* antibodies in the blood does not protect against a new *Borrelia burgdorferi* sensu lato infection because of strain variability. Performing a serological test at four weeks in patients presenting with reinfection may help detect increased IgG levels. Clinical signs and symptoms, exposure to tick bites, culture, and molecular biology – depending on the localization – may help guide the diagnosis in the absence of elevated IgG levels. A positive serology result does not distinguish an active infection from a serological scar [17]. A positive serology result without any clinical signs and symptoms is either suggestive of a serological scar or an asymptomatic seroconversion indicating contamination but not active Lyme borreliosis. A Swiss longitudinal study (1986-1993) of 305 patients infected with *Borrelia burgdorferi* sensu lato, with a positive Lyme serology but without any initial clinical signs, reported that more than 95% of patients remained asymptomatic at seven years of follow-

up [2]. A prospective Scandinavian study showed that, in the absence of prophylaxis and within three months following a tick bite, 5.4% of patients (102/1,886) achieved seroconversion, with clinical signs of Lyme borreliosis in 39.2% of cases (40/102) [18].

- The sole persistence of IgM beyond six weeks should be considered a false positive result, because of the high risk of non-specific cross-reactions.
- Performing a serological test at four weeks in patients presenting with reinfection may help detect increased IgG levels.
- A positive serology does not distinguish an active infection from a serological scar.
- High levels of antibodies can be observed in treated patients several years after recovery. The treatment should in that case not be resumed.

1.2 Diagnosis by polymerase chain reaction (PCR)

Could *Borrelia burgdorferi* DNA PCR detection be suggested? The specificity of the test should be close to 100% – which is not always the case depending on the manufacturer as the targets, primers, and manufacturer's methods are neither standardized nor assessed. A positive PCR result for *Borrelia burgdorferi* sensu lato does not establish active infection [19]. The PCR sensitivity varies depending on the disease stage and its localization [15]. PCR testing is useful for difficult-to-establish diagnoses when cutaneous (PCR test on skin biopsy) or joint manifestations (PCR test on synovial fluid or synovial biopsy) are observed. It is however pointless in patients presenting with neurological manifestations for more than six weeks (poor sensitivity) [1]. Looking for *B. burgdorferi* sensu lato by PCR test in urine and blood samples is not recommended as available studies reported highly contradictory results [5, 15].

1.3 Culture and histology

Culture is the reference biological diagnostic method, with 100% specificity but with limited sensitivity because of the small number of bacteria at the sampling sites [5, 20]. There is no healthy carriage of *Borrelia burgdorferi* sensu lato: isolation of the bacterium indicates active Lyme borreliosis. Culture is performed in specialized laboratories. The culture medium is specific (BSK), enriched, and it may easily be contaminated by commensal bacteria. Culture takes time (usually 2-8 weeks), and negative results are available only after three months. Spirochetes cannot be detected by Gram staining at direct microscopic examination. A dark-

field or phase-contrast microscope is required or direct immunofluorescence should be used (moderate sensitivity and specificity). Official identification of the bacterium is then performed by molecular biology. Microscopy can be used to interpret culture results, but direct microscopy on samples is not recommended because of its lack of specificity. Histology is useful for the diagnosis of ACA and for differential diagnoses, but the result is not indicative of active Lyme borreliosis [21].

1.4 Other biological tests

1.4.1 Tests under evaluation: CXCL13 level in CSF

This test has 89-97% sensitivity and 92-98% specificity in Lyme neuroborreliosis [22, 23].

1.4.2 Diagnostic methods not recommended for Lyme borreliosis, because of a lack of sensitivity and/or specificity [5]

– thin blood film-thick blood smear

– Dark-field microscopy or phase-contrast microscopy

– CD57+/CD3-NK cell level

– Rapid diagnostic tests

– *Borrelia* PCR in blood and/or urine

– *Borrelia* PCR in CSF if symptom onset >6 weeks.

1.4.3 Diagnostic methods not recommended for Lyme borreliosis, because of a lack of study or contradictory study findings [5]

– Lymphocyte transformation tests (LTT) and searching for interferon-gamma and interferon-alpha indirect markers

– Xenodiagnosis

– Membrane protein level

– CCL19, apolipoprotein B-100

New tests will need to be assessed as part of prospective studies in the future reference centers. Results will be published and evaluated by the ANSM and the CNRs for the relevant pathogens ***(grade AE)***.

1.5 Imaging tests

No radiological lesion is indicative of Lyme borreliosis. Imaging tests are mainly used to investigate a differential diagnosis.

2. Treatment

2.1 Erythema migrans and borrelial lymphocytoma

2.1.1. Erythema migrans and multiple erythema migrans (Table 3)

Erythema migrans is self-limiting without treatment (within a few weeks), but *Borrelia burgdorferi* sensu lato may persist in the skin [24] and new manifestations may occur later on. An antibiotic therapy is therefore required, with documented efficacy, irrespective of symptom duration before treatment. Twenty studies compared several molecules with various treatment durations, dosing regimens, and outcomes. Antibiotics with proven efficacy are doxycycline, amoxicillin, cefuroxime-axetil, ceftriaxone, azithromycin, phenoxymethylpenicillin, and minocycline [25]. A meta-analysis suggested the absence of difference in efficacy and tolerability between molecules, with low rates of treatment failure (4% at 2 months, 2% at 12 months) [26]. Considering the continuum between early localized and disseminated manifestations and the efficacy of doxycycline in patients presenting with Lyme neuroborreliosis [27], doxycycline should be favored as first-line treatment ***(grade B)***.

Erythema migrans is usually cured after 7 to 13 days of an appropriate antibiotic therapy. A clinical follow-up is required ***(grade A)***. The diagnosis of erythema migrans should be questioned if lesions persist ***(grade A)*** [25, 27]. Non-specific signs may however persist for several months, but they usually disappear within one year in most patients [28, 29]. Their persistence should not lead to prescribing a new antibiotic therapy ***(grade A)***. However, patients should be informed that they need to consult in case of new symptom onset as the infection is not immunizing ***(grade A)***. A 14-day treatment duration is recommended in cases of erythema

migrans or multiple erythema migrans, whether or not associated with non-specific symptoms (***grade B***).

2.1.2. Borrelial lymphocytoma (Table 3)

A retrospective non-comparative study of 144 adult patients presenting with borrelial lymphocytoma treated with amoxicillin, doxycycline, cefuroxime-axetil, azithromycin, or phenoxymethylpenicillin for 14 days reported that a second antibiotic therapy was required for 14 patients (9.7%), because of an initial treatment failure (persistence of the lesion for more than one month after treatment, new signs of Lyme borreliosis, or persistence of clear non-specific signs and symptoms). The main risk factor for treatment failure was the presence of signs suggestive of dissemination. The outcome was favorable for all patients at one year, with disappearance of the lymphocytoma within 21 days on average (10-30 days) [30]. Recent guidelines from other countries recommend the use of amoxicillin 1 g thrice daily or doxycycline 200 mg/day for 21 days [1, 31, 32]. Only the Belgian guidelines recommend a shorter treatment with doxycycline for 10 days or amoxicillin for 14 days.

The first-line treatment of borrelial lymphocytoma is doxycycline (alternative: amoxicillin), at the same dosage as for erythema migrans and for 21 days *(**grade B**)*. Children can alternatively be treated with azithromycin for 10 days.

2.2 Lyme neuroborreliosis

The antibiotic therapy of Lyme neuroborreliosis has never been evaluated in placebo-controlled studies. The Cochrane Library retrieved seven European randomized studies [33-40], including a pediatric study [37], assessing penicillin G, cefotaxime, ceftriaxone, and doxycycline for 10 to 21 days. An open-label randomized study did not report any difference between a 14-day regimen and a 28-day regimen with ceftriaxone [41]. A retrospective cohort study of early Lyme borreliosis manifestations, mainly cutaneous but also neurological manifestations, did not show any difference between treatment durations of less than 10 days and more than 16 days [42]. A non-inferiority, multicenter, randomized, placebo-controlled, blinded study is currently ongoing to compare two weeks with six weeks of doxycycline. A study demonstrated the non-inferiority of doxycycline (200 mg/day) versus ceftriaxone

(2 g/day) for early disseminated manifestations [27]. The studies included few late manifestations (10%) and specific analyses were not performed. Adverse effects of ceftriaxone, mainly due to the parenteral route of administration or its broad spectrum, should lead physicians to favor doxycycline for the treatment of Lyme neuroborreliosis [43] ***(grade AE).***

The evidence-based German guidelines recommend ceftriaxone or doxycycline during 14 days for early Lyme neuroborreliosis and during 14 to 21 days for late Lyme neuroborreliosis (Table 4). A review of available pediatric data resulted in the same suggestions [44]. The British guidelines make a distinction between central and peripheral symptoms: oral doxycycline or amoxicillin treatments are recommended for cranial nerve symptoms and/or peripheral nervous system symptoms. Ceftriaxone or doxycycline are recommended in patients presenting with central nervous system symptoms, with increased doses of doxycycline at 200 mg twice daily in case of encephalitis, myelitis, or vasculitis. The British guidelines recommend 21 days of treatment for all manifestations of Lyme neuroborreliosis. Adjuvant corticosteroid therapy is not recommended for patients presenting with radiculalgia and is most likely harmful to patients presenting with facial palsy associated with early Lyme neuroborreliosis [45]. Jarisch-Herxheimer reaction has never been reported in European studies of Lyme neuroborreliosis since 1990. Corticosteroids are not recommended in patients presenting with neurological manifestations of Lyme borreliosis ***(grade C).***

Risk factors for quality of life impairment and fatigue following treatment for Lyme neuroborreliosis have been identified in a cohort of 50 patients followed for 30 months [46]: time to treatment initiation >6 months after symptom onset, severe initial neurological manifestations, and residual symptoms at four months (28% of patients, especially if the diagnosis is uncertain) [47]. These arguments lead to recommending a 21-day treatment when time to treatment initiation is superior to six months and a 14-day treatment when time to treatment initiation is inferior to six months ***(grade B).*** Symptom resolution may take time, up to several years after treatment, especially when treatment is initiated late. Sequelae such as residual pain may persist and should not be considered indicative of bacterial resistance. Ninety per cent of patients treated for Lyme neuroborreliosis with peripheral neuropathy usually no longer have symptoms at 5 years, and 10% have sequelae such as neuropathic pain or sensory deficit [47]. A large-scale study of 2,067 patients presenting with confirmed Lyme neuroborreliosis in Norway compared various indicators collected five years after treatment with the indicators of 20,670 paired controls. No significant difference was observed in the

long-term survival, health status, or social functioning. Such findings document the excellent long-term prognosis in appropriately treated patients [48].

Cyclines are usually contraindicated in children below 8 years of age, because of the risk of permanent tooth coloration and enamel hypoplasia reported with tetracycline. This adverse effect has not been reported with doxycycline, and some studies reported its good tolerability in children [49]. Treatment with doxycycline could thus be discussed, especially when beta-lactams are contraindicated or when the IV line is difficult to insert or manage, after having informed the parents that such treatment does not have a marketing authorization in France for use in children below 8 years of age ***(grade AE)***.

2.3 Joint manifestations of Lyme borreliosis (Table 5)

Few studies have been performed to evaluate the treatment of joint manifestations of Lyme borreliosis. Most of these studies are relatively old, observational, or with a small sample size. They are based on long-term follow-up (>12 months) [50, 51]. The inclusion criteria of these studies are usually non-specific joint signs associated with positive serology. Some of the included patients may not have had active Lyme borreliosis.

Amoxicillin, only evaluated as a combination with probenecid, showed equivalent efficacy to doxycycline over a 30-day period. Some patients receiving amoxicillin/probenecid developed neurological signs attributed to Lyme neuroborreliosis after treatment [50]. The administration of third-generation injectable cephalosporins for 14 days was associated with equivalent efficacy or was even superior to intravenous penicillin G for 10 days. Ceftriaxone (2 g/day) was the most evaluated drug, including in children. An oral cephalosporin (cefixime) showed lower efficacy than ceftriaxone [52]. A retrospective study of 24 patients, with a mean follow-up of 40 weeks, treated with doxycycline (200 mg/day for 30 days), oral amoxicillin-clavulanic acid (2 g/250 mg per day for 30 days) or IV amoxicillin-clavulanic acid (1 g/200 mg thrice daily for 21 days), or ceftriaxone (2 g/day for 14 days), reported that four patients received a second antibiotic therapy and nine patients an intra-articular injection of corticosteroids or underwent synovectomy. All patients were cured [51]. Another retrospective study of 26 patients treated with ceftriaxone 2 g/day for 14 days, with a three-year follow-up, reported a good response in 19 patients, relapse in six patients, and new manifestations in four patients [53]. An open-label randomized study comparing 14 vs 28 days of ceftriaxone reported 5/80 treatment failures in the 14-day group vs. 0/63 in the 28-day group

(p=0.07). However, a higher number of adverse effects was reported in the 28-day group (p=0.02) [41]. The analysis of published studies comparing doxycycline and ceftriaxone using efficacy, tolerability, and cost criteria, leads to favoring doxycycline for Lyme arthritis ***(grade AE)***.

Several studies suggested that corticosteroid administration was harmful to patients, although with a low level of scientific evidence [50]. Intra-articular injections of corticosteroids are possible, provided appropriate antibiotic therapy has already been initiated [50] ***(grade AE).*** Randomized studies rarely reported an initial treatment success rate of 100% [50]. A second antibiotic therapy course sometimes leads to cure. Clinical experience reveals that persistent arthritis after two lines of treatment is usually related to a reactive arthritis with a potential progression to inflammatory rheumatism, and should be managed as such.

Patients presenting with persistent arthritis after two lines of adequate treatment and with a negative PCR in synovial fluid should be referred to a rheumatologist or a pediatrician for the management of reactive arthritis and to discuss progression to inflammatory rheumatism ***(grade AE)***.

2.4. Acrodermatitis chronica atrophicans (ACA)

A prospective cohort study of 46 patients, including various treatments, reported an almost systematic cure with 30 days of doxycycline 200 mg/day (n=6/6) or with 30 days of phenoxymethylpenicillin 1.5 M IU thrice daily (n=13/14, one patient presented with persistent arthralgia) [54]. Lower-quality studies reported failures with treatment duration shorter than 28 days. Skin atrophy is irreversible, but allodynia usually rapidly resolves. Moderate sensory deficit may persist.

ACA should be treated with doxycycline 200 mg/day for 28 days. Another option is IV ceftriaxone 2 g/day for 28 days ***(grade B)***. ACA-associated neuropathic pain should not impact the treatment choice ***(grade AE)***. Support stockings may be suggested to patients presenting with ACA-related edema on a lower limb ***(grade AE)***. Slow resolution of inflammatory cutaneous signs (erythema, edema), that may take more than six months, does not provide grounds for the initiation of a new antibiotic treatment ***(grade AE)***.

2.5 Ophthalmologic manifestations of Lyme borreliosis (Table 6)

Treatment of lesions localized on the eyes surface (except for keratitis) is based on doxycycline (200 mg/day) or ceftriaxone (2 g/day) for 14 days ***(grade AE)***. Treatment of keratitis and intraocular, orbital, and neuro-ophthalmologic presentations is based on data originating from Lyme neuroborreliosis, but with ceftriaxone for 21 days as first-line regimen, because of the poor intraocular penetration of doxycycline ***(grade AE)***. A corticosteroid therapy (topical, periocular, intravitreous, or systemic) is frequently prescribed in combination with ceftriaxone – despite the lack of robust evidence – at decreasing doses depending on the treatment response and surveillance criteria (biomicroscopy, angiography, optical coherence tomography). Prescribing a new course of antibiotics to patients with high-dose corticosteroid dependence or relapse should be discussed on a case-by-case basis.

Adjuvant corticosteroid therapy may be prescribed if the ocular inflammation persists. The administration route depends on the type of impairment (***grade AE***).

2.6 Cardiac manifestations of Lyme borreliosis

Available data is derived from a systematic literature review of type 3 atrioventricular blocks (AVB) in Lyme borreliosis [55], and from a retrospective study [56]. The most important study was performed in the United States and included 45 patients presenting with type 3 AVB associated with Lyme borreliosis. Patients were treated with IV ceftriaxone (47% of cases) or with an oral antibiotic therapy (penicillin or tetracycline, 35% of cases). Forty per cent of patients required temporary cardiac pacing and 4% long-term cardiac pacing [55]. Hospitalization with continuous monitoring is recommended in cases of syncope, dyspnea, chest pain, type 2 or 3 AVB, or type 1 AVB when the PR interval is >30 ms (risk of rapid worsening) [39]. AVB, even complete, usually resolves within one week [55].

Patients presenting with syncope, type 2 or 3 AVB, or type 1 AVB >30 ms ***(grade C)*** should receive an initial treatment with IV ceftriaxone (2 g daily for adults), with a switch to oral doxycycline (100 mg twice daily for adults) or amoxicillin (1 g thrice daily for adults) as soon as continuous monitoring is no longer required, for a total duration of 21 days **(*grade AE*)**. Doxycycline or amoxicillin may be used for the first-line treatment of patients presenting with other manifestations ***(grade C)***.

The use of temporary cardiac pacing may be indicated, as per the specialist's advice. Long-term cardiac pacing is not recommended in the first-line setting ***(grade AE)***. Chronic dilated cardiopathy associated with a history of Lyme borreliosis should not be treated with an antibiotic therapy in the absence of causal link ***(Grade C)***.

2.7. Specific situations (sexual transmission, pregnant women, breastfeeding women)

Sexual transmission of Lyme borreliosis has been suggested, but has never been proven [57]. Mother-to-fetus transmission of Lyme borreliosis has been suggested based on autopsy results, but no causal link has been evidenced with pregnancy outcome [58]. A literature review identified 45 studies (including 29 clinical cases or case series), with numerous biases (small sample size, non-approved diagnostic tests, etc.) and conflicting results. No conclusion can therefore be drawn on the risk for fetuses [59]. A meta-analysis of nine studies reported fewer adverse effects (miscarriage, fetal death in utero, etc.) in women treated for Lyme borreliosis during pregnancy (11%, 95% CI 7-16) than in non-treated women (50%, 95% CI 30-70) [59]. A study reported two cases with positive *Borrelia* PCR in the breast milk of breastfeeding women (in-house PCR test, not approved in breast milk), without any consequence for the newborns [60].

Pregnant women presenting with Lyme borreliosis should be treated as per the same modalities as the general population, without any delay (***grade A***). Amoxicillin or ceftriaxone is to be favored as first-line treatment, depending on the disease stage ***(grade B)***. Doxycycline administered after the first trimester of pregnancy is associated with a risk of coloration of deciduous teeth, with no impact on permanent teeth (http://www.lecrat.fr) ***(grade B)***.

2.8. Prolonged treatment or re-treatment

Five placebo-controlled randomized trials have been performed with patients presenting with prolonged symptoms (asthenia, arthralgia, neuropathic pain, cognitive disorders, etc.) following adequately treated Lyme borreliosis [38, 61-64]. The assessed treatments, sometimes as part of a combination, were IV ceftriaxone for two to four weeks (n=4), doxycycline (n=4), and clarithromycin-hydroxychloroquine combination (n=1). All these trials demonstrated a substantial placebo effect, without any additional benefit of the antibiotic therapy in terms of

quality of life, pain, or fatigue. One study reported significant differences in terms of pain and fatigue at 12 weeks, but not at 24 weeks. These studies also evidenced the adverse effects of prolonged antibiotic therapies, sometimes severe (*Clostridium difficile* colitis, venous line complications) [65]. Such an inappropriate use of antibiotics has an ecological impact. In a 2015 report the ANSM classified ceftriaxone as an antibiotic highly contributing to the emergence of resistance.

Patients presenting with persistent symptoms after adequately treated Lyme borreliosis should not receive repeated or prolonged courses of antibiotics (***grade A***).

3. Persistent symptoms after documented or suspected Lyme borreliosis

Some patients present with persistent and pleomorphic symptoms (asthenia, arthralgia, myalgia, headaches, cognitive disorders, paresthesia, etc.) with functional impact, attributed to Lyme borreliosis, other tick-borne diseases, or even a co-infection. This category of patients includes patients who have been adequately treated for documented Lyme borreliosis but who no longer present objective signs of an active infection, as well as treated or untreated patients consulting for a suspicion of Lyme borreliosis (unconfirmed). Symptoms are attributed to Lyme borreliosis by a relative or by the patient himself, often after having searched the Internet. Northern American studies initially made a distinction between these two types of patients, but we believe they should be grouped together as they share the same signs and symptoms, some underlying pathophysiological mechanisms, and management modalities [66-68].

3.1 Epidemiological approach

Six studies performed in the United States [66, 67], Netherlands [68], and France [69-71] included more than 2,000 patients consulting for a suspicion of Lyme borreliosis and reported similar results. The three French studies – the most recent – included more than 1,000 patients, of whom only 12% (Besançon), 13% (Paris), and 15% (Nancy) were finally diagnosed with confirmed or probable Lyme borreliosis following investigations. Up to 80% of patients actually received another diagnosis, with a potential loss of chance for appropriate care because of diagnostic delay, and up to 85% of patients received a pointless antibiotic therapy (sometimes for years). The care pathway of patients presenting with a suspicion of Lyme borreliosis has already been properly assessed in Nancy [70]. Following the initial consultation, 75% of patients were referred to specialists for the diagnosed disease and 25% underwent further investigation.

The three French studies confirmed the wide range of differential diagnoses already described in the United States in the 1990s [72]: neurological diseases (12-19%), rheumatologic diseases (15-43%), psychiatric or psychological diseases such as burn out syndrome (13-25%), or systemic/autoimmune diseases (Table 7). The proportion of undetermined diagnoses (10%) reaches 50% when the diagnosis of "persistent somatic symptoms" is not taken into consideration. Persistent somatic symptom disorder has long been recognized, although under various names [73]. It is characterized by: *i)* chronic and incapacitating physical symptoms that cannot be entirely attributed to anatomical lesions, and *ii)* specific cognitive and behavioral symptoms. When the physical symptoms mainly belong to a single entity, they may lead to the specific diagnosis of functional somatic syndrome (e.g., fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome). When these symptoms belong to several entities, as most frequently observed, a general diagnosis is more appropriate: "somatic symptom disorder" (*American Psychiatric Association*), "bodily distress syndrome" (World Health Organization), or "persistent somatic symptoms" (*European Association of Psychosomatic Medicine*) [74]. The latter term (persistent somatic symptoms) seems more appropriate ***(grade AE)***. These disorders account for 36% and 56% of diagnoses received by patients consulting for a suspicion of Lyme borreliosis in the two American studies performed in the 1990s [66, 67]. Their prevalence is estimated at 6% of the general population and they account for 16% of primary care consultations and for up to 33% of specialized consultations [75].

3.2. Diagnostic strategy

3.2.1. Initial consultation

Thorough anamnesis and comprehensive clinical examination are required. A global strategy is required to take into consideration the context, the patient's environment, and pathway ***(grade AE)***. Sufficient time should be dedicated to this initial consultation, and/or it should be divided into several consultations ***(grade AE)***. The anamnesis should go through the following steps: *i)* let the patient tell the "disease story" that led him to suspect he may have Lyme borreliosis; *ii)* list all arguments developed by the patient in favor of Lyme borreliosis diagnosis; *iii)* assess the patient's conviction related to the Lyme borreliosis diagnosis (the physician may ask the patient to grade this likelihood using percentages); *iv)* try to understand if alternative hypotheses have been suggested by the patient's physicians, relatives, or by the patient and why the patient believes these alternative hypotheses are less likely; *v)* assess the reported symptoms, their progression over time, the aggravating or relieving factors, and list in order of importance

those with the strongest negative impact on the patient's quality of life (e.g., fatigue, widespread pain, etc.) ***(grade AE)***.

The clinical examination should be thorough and comprehensive. It should focus on rheumatologic, neurological, dermatological, and psychiatric signs and symptoms ***(grade AE)***. Emotional distress should be assessed, mainly anxious and depressive symptoms. Panic attacks should particularly be looked for among anxious symptoms, especially if symptom onset occurred after an attack. Excessive fear of diseases, insensitive to reassuring arguments, should also be looked for. Patients should be informed that at this stage the aim is not to find a causal link between physical and psychological symptoms, that may either be causes or consequences – most often both – because of circular causality. Vicious circles contributing to the persistence of symptoms involve brain mechanisms (central sensitization, psychological conditioning), somatic mechanisms (physical deconditioning), and social mechanisms (healthcare system organization, role of the media, conspiracy theories). These mechanisms are targeted by the proposed treatments.

Physicians should verify that the initial examinations have been performed before deciding on further examinations. However, biological and radiological examinations aiming at ruling out unlikely diagnoses should not be prescribed in excess – at the risk of fortuitous discoveries (biological or imaging results with no clinical significance) – as they are likely to lead to wrong diagnoses and to reinforce the patient's worries and conviction of being sick ***(grade AE)***. Even prescribing routine investigations may reinforce the patient's conviction that the diagnosis is uncertain and that further examinations are required. Physicians should ask themselves the following question: "Would I prescribe this investigation if the patient was not so worried?". If the answer is no, the investigation should be postponed. All investigations performed – whether it be positive, negative, or artefact – should be taken into account. Tests previously performed (serology, immunology, toxicology, etc.) should not be ruled out or disregarded, because the patient invested faith and money in them: he should not be held responsible or be considered a stakeholder in the current medical and media controversy. The diagnostic work-out should be guided by symptoms and by the physical examination and investigations already performed ***(grade AE)***.

3.2.2. Diagnostic process

Fever or inflammation is not suggestive of Lyme borreliosis diagnosis and should rather lead to suspect other infectious or systemic diseases ***(grade AE)***. Numerous pathologies may be

responsible for widespread pain. Objective physical signs should lead physicians to considering other organic diseases and may require a specialist's advice (Table 7). Persistent somatic symptoms should be considered when no objective signs are observed ***(grade AE)***. This diagnosis should however not be an exclusion diagnosis. It should be a truly positive diagnosis based on the identification of cognitive symptoms (hypothesis of a sole somatic etiology, belief in the increasing severity or impact of symptoms, absence of reassuring effect brought by the normal results of the investigations performed), and behavioral symptoms (avoiding talking about the context of physical symptom onset, numerous consultations and investigations performed). Patients often find it difficult to hear that "as their test results are absolutely fine, the diagnosis should be…". It is much better to explain that the clinical symptoms are "highly suggestive of persistent somatic symptoms".

3.3. Treatment strategy

The management of rheumatologic, neurological, cardiac, dermatological, inflammatory, and psychiatric diseases should be performed by the corresponding specialists and physicians specialized in pain management ***(grade AE)***. In some countries the management of persistent somatic symptoms falls under a specific medical specialty, i.e. psychosomatic medicine. This specialty does not exist in France, but other specialists (general practitioners, rheumatologists, internal medicine physicians, psychiatrists, etc.) have expertise in this area.

The management of persistent somatic symptoms is based on various elements ***(grade AE)***:

1/ Patients should be informed that the reported symptoms (fatigue, pain, etc.) are non-specific and that they may be due to several causes (for instance for prolonged asthenia: mild somatic disease, stressful or tiring lifestyle, deconditioning to physical exercise, emotional distress, sleep disorders, etc.).

2/ Physicians should avoid excessive and stigmatizing simplifications as they may be understood as "it's all in your head". They should rather focus on more elaborated and customized explanations, drawing on circular causal links [76].

3/ Physicians should clearly identify the patient's predisposing factors (psychological and somatic vulnerability), precipitating factors (including infectious factors or even Lyme borreliosis in case of positive serology), and factors contributing to the persistence of symptoms involving avoidance mechanisms and social reinforcing factors. Only the factors contributing to the persistence of symptoms can be managed by a medical treatment.

4/ Physicians should clearly explain why, from a medical standpoint, the hypothesis of active Lyme borreliosis can only be considered as a potential precipitating factor in case of a history of Lyme borreliosis, to explain the patient's current symptoms.

5/ Physicians should explain the lack of benefit of prolonged antibiotic therapies (disappearance of the triggering factor, no proof of efficacy in high-quality control studies). To remain consistent and credible, physicians should not suggest an antibiotic therapy just to give the impression of having heard the patient and to pretend to have met their expectations, and even less with the intent to show that the antibiotic therapy is pointless. Such treatments may lead to improvement, but it will be incomplete and not different from that observed with a placebo [61]. Besides, these treatments are associated with risks and with the selection of bacterial resistance.

6/ Physicians should suggest alternative customized explanations for the patient's symptoms (neglected somatic diseases, lifestyle, emotional distress, biological and behavioral vicious circles contributing to the persistence of symptoms). The following factors contributing to the persistence of symptoms should be addressed: difficult relations with the healthcare system (feeling of lack of recognition from healthcare professionals, with a potential lack of knowledge of the persistent somatic symptom diagnosis), worrying doubts conveyed by the Internet.

7/ Physicians should suggest a positive diagnosis. As there is no consensus on the preferred term, the choice should be based on the term compatibility with the patient's ideas and should aim to putting an end to medical nomadism. Physicians should strive to achieve a joint decision with the patient. Establishing a specific diagnosis may meet such criteria if the symptoms belong to a specific entity (e.g., fibromyalgia). Otherwise, physicians should use one of the three globally accepted terms: somatic symptom disorder, bodily distress syndrome, or persistent somatic symptoms [74]. The generic term of "functional disorder" is also well-accepted. Besides the positive wording of the diagnosis, the patient is more likely to accept it when physicians mention that such disorder is quite frequent. Physicians should acknowledge the grueling nature of the patient's symptoms as well as the resulting incapacity when no diagnosis is established. Focus should also be put on the availability of various treatments, resulting from various researches. Physicians should however remain cautious about treatment effects and emphasize that the treatment aims at relieving symptoms and improving the patient's quality of life rather than curing the patient, especially if the patient has been complaining of such symptoms for a while. However, complete resolution may be obtained, especially in cases of recent disorder onset.

8/ Physicians should write a detailed letter [77], that will be sent to the patient and their physicians. The letter should include all items discussed with the patient, arguments related to

alternative causes of the symptoms, the final diagnosis, and the benefit in limiting further investigations.

9/ Physicians should suggest a follow-up consultation to establish a joint therapeutic agenda between patient and physician and clearly explain that they are ready to take responsibility for the choices and decisions taken, and even for the risk of making a mistake.

10/ If the patient is not reluctant to the potential role of cognitive and behavioral factors in the persistence of symptoms, physicians should suggest a behavioral and cognitive therapy [78]. Patients should however be informed that such treatment is not reimbursed in France when performed by psychologists.

Conflict of interests

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Table 1. Performance of diagnostic tests (sensitivity/specificity) in European Lyme borreliosis
Tableau 1. Performances des tests diagnostiques (sensibilité/spécificité) dans la borréliose de Lyme européenne

Clinical suspicion	ELISA	Sensitivity ELISA	Specificity ELISA	PCR	Other useful examinations
Tick bite	Not useful	/	/	/	No
Erythema migrans	Not recommended	IgG: 36% (29-43) IgM: 42% (36-49)	IgG: 96% (94-97) IgM: 95% (92-97)	PCR on skin biopsy: Sensitivity 69% (35-81)	PCR on skin biopsy
Early Lyme neuroborreliosis <6 weeks	IgG + IgM	67-85%	92-97%	PCR in CSF: variable sensitivity	Intrathecal synthesis (antibody index) CSF cytology (lymphocytosis)
Semi-early neuroborreliosis, 6 weeks-6 months	IgG + IgM	90-99%	92-97%	PCR in CSF: not useful	Intrathecal synthesis CSF cytology (lymphocytosis)
Borrelial lymphocytoma	IgG + IgM	≥80%	92-97%	PCR on skin biopsy	Histology
Late Lyme neuroborreliosis >6 months	IgG	99%	92-97%	PCR in CSF: not useful	/
Lyme arthritis	IgG	IgG: 94% (86-98) IgM: 39% (28-52)	IgG: 97% (94-98) IgM: 95% (88-98)	PCR in synovial fluid: sensitivity 36-85%	PCR in synovial fluid and/or synovial biopsy
Ocular symptoms	IgG + IgM	Variable depending on the manifestations	92-97%	PCR in aqueous humor, CSF (variable sensitivity)	Intrathecal synthesis CSF cytology (lymphocytosis)
Cardiac symptoms	IgG + IgM	>80%	92-97%	/	No

Acrodermatitis chronica atrophicans	IgG	IgG: 99% (82-99) IgM: 18% (9-34)	IgG: 97% (95-98) IgM: 97% (93-98)	PCR on skin biopsy: sensitivity 16-92%	Histology

CSF: cerebrospinal fluid

Table 2. Performance of diagnostic tests for the other tick-borne diseases
Tableau 2. Performances des tests diagnostiques dans les autres maladies vectorielles à tiques

Clinical suspicion	Serology	Serological diagnostic criteria	Serology specificity	PCR	Other useful examinations	Examinations that should not be performed
Tick-borne encephalitis [30]	IgG + IgM	IgM and IgG Seroconversion or increased IgG levels (Grade A, I)	Cross reactions: other arboviroses, yellow fever vaccine (IgG)	Only at the initial stage (viremia)	CSF: cytology (monocytosis) + IgM	Urine PCR
Human granulocytic anaplasmosis [31–38]	IgG, IgM, or TIg	Increased TIg or seroconversion, Se: 32% High levels of TIg Se: 58% (Grade B, II)	97%	PCR on whole blood, viremic stage Se: 74%, Sp: 100%	Thin blood film (detection of morula) Se: 20%	/
Babesiosis [38]	IgG + IgM, or TIg	Seroconversion or increased TIg: Se: unknown	Unknown	PCR on whole blood at the febrile stage	Thin blood film (detection of trophozoites)	Dark-field microscopy or phase-contrast microscopy
Borrelia miyamotoi [39]	-	/	/	PCR on whole blood at the febrile stage	/	Thin blood film - thick blood smear
***Candidatus* Neoehrlichia mikurensis** [40]	-	/	/	PCR on whole blood at the febrile stage	/	Thin blood film - thick blood smear
Mediterranean spotted fever [41,42]	IgG + IgM	Seroconversion or increased TIg, Se: 100% after Day 30 (Grade A, I)	Risk of cross reactions between species	PCR on black spot		/

Francisella tularensis [43,44]	IgG or TIg	Seroconversion or increased IgG levels Se: 100% after Day 30	Cross reactions in IgM	PCR on ulcer or lymph node, Se: 75%	/	/

Se: sensitivity; Sp: specificity; CSF: cerebrospinal fluid; TIg: total immunoglobulins (G and M)

Table 3. Treatment of erythema migrans (single or multiple) and of borrelial lymphocytoma

Tableau 3. Traitement de l'érythème migrant, unique ou multiple, et du lymphocytome borrélien

ANTIBIOTICS		DOSING REGIMEN	DURATION
Adults and children from 8 years of age			
1st line	Doxycycline	100 mg twice daily Children: 4 mg/kg/day as two intakes (maximum 100 mg/intake, and 200 mg/day)	14 days for erythema migrans, 21 days for borrelial lymphocytoma
2nd line	amoxicillin	1 g thrice daily Children: 50 mg/kg/day as three intakes, every 8 hours if possible* (maximum 1 g per intake)	
Children <8 years of age			
1st line	amoxicillin	50 mg/kg/day as three intakes, every 8 hours if possible*	14 days for erythema migrans, 21 days for borrelial lymphocytoma
2nd line	azithromycin	20 mg/kg/day without exceeding 500 mg/day	5 days for erythema migrans, 10 days for borrelial lymphocytoma

* If the 8-hour interval between each intake is not possible, 25 mg/kg every 12 hours

Table 4. Treatment of Lyme neuroborreliosis
Tableau 4. Traitement des neuroborrélioses

Antibiotics	**Adults**	**Children**	**Duration**
Early Lyme neuroborreliosis (symptom onset <6 months)			
Doxycycline	100 mg twice daily	From 8 years of age: 4 mg/kg/day (maximum 200 mg/day) as two intakes	14 days
IV ceftriaxone	2 g once daily	80 mg/kg once daily (maximum 2 g)	14 days
Late Lyme neuroborreliosis (symptom onset >6 months)			
Doxycycline*	100 mg twice daily 200 mg twice daily in case of central nervous system impairment**	From 8 years of age: 4 mg/kg/day (maximum 200 mg/day) as two intakes 8 mg/kg/day (maximum 400 mg/day) as two intakes in case of central nervous system impairment**	21 days
IV ceftriaxone	2 g once daily 80 mg/kg once daily in case of central nervous system impairment,** as one or two administrations	80 mg/kg once daily (maximum 2 g) 80 mg/kg once daily in case of central nervous system impairment,** as one or two administrations	21 days

*****Some studies showed the good tolerability of doxycycline as a short treatment (≤14 days) in children below 8 years of age. Treatment with doxycycline could be discussed on a case-by-case basis in children, especially when beta-lactams are contraindicated or when the IV line is difficult to insert or manage, after having informed the parents that such treatment does not have a marketing authorization in France for use in children aged below 8 years.

** Central nervous system impairment = encephalitis, myelitis, vasculitis.

Table 5. Treatment of joint manifestations of Lyme borreliosis
Tableau 5. Traitement des manifestations articulaires de la borréliose de Lyme

Antibiotics	**Adults**	**Children**	**Duration**
Oral doxycycline* as first-line treatment	100 mg twice daily	From 8 years of age: 4 mg/kg/day (maximum 200 mg/day) as two intakes	28 days*
IV ceftriaxone, 2nd line, in case of failure or contraindication to doxycycline	2 g once daily, IV	80 mg/kg once daily (maximum 2 g)	
Oral amoxicillin as third-line treatment	1 g thrice daily	80 mg/kg/day as three intakes (maximum 3 g)	

* When the first-line antibiotic therapy has failed, the parenteral route should be favored for the second-line antibiotic therapy

Table 6. Treatment of ophthalmologic manifestations of Lyme borreliosis

Tableau 6. Traitement des manifestations ophtalmologiques de la borréliose de Lyme

Antibiotics	**Adults** **Dose/day**	**Children** **Dose/kg/day**	**Duration**
Surface lesions, except for keratitis: conjunctivitis, episcleritis			
Oral doxycycline	100 mg twice daily	From 8 years of age: 4 mg/kg/day (maximum 200 mg/day) as two intakes	14 days
IV ceftriaxone	2 g once daily	80 mg/kg once daily (maximum 2 g/day)	14 days
Keratitis, scleritis, uveitis, retinitis, optical neuropathy, oculomotor nerve palsy, orbitopathy			
IV ceftriaxone	2 g once daily 80-100 mg/kg/day in case of central nervous system impairment	80 mg/kg once daily	21 days
Oral doxycycline (2^{nd} line)	100 mg twice daily 200 mg twice daily in case of central nervous system impairment	From 8 years of age: 4 mg/kg/day (maximum 200 mg/day) as two intakes	21 days

Table 7. Possible causes of persistent symptoms after documented or suspected Lyme borreliosis
Tableau 7. Causes possibles des symptômes persistants au décours d'une borréliose de Lyme documentée ou suspectée

Bone and joint diseases	- Mechanical diseases: • Arthritis/osteomyelitis of the limb and/or vertebral osteomyelitis (with potential complications such as lumbar or cervical stenosis) • Tendinopathy or bursopathy, that may be occupational - Inflammatory diseases: • Spondyloarthritis • Rheumatoid arthritis • Crystal arthropathy: gout, chondrocalcinosis
Muscular diseases	- Inflammatory myopathies (polymyositis, dermatomyositis, inclusion-body myositis) - Genetic myopathies - Iatrogenic myopathies (lipid-lowering agents, fluoroquinolones)
Neurological diseases	- Peripheral neuropathy: diabetes, alcohol, vitamin deficiency, amylosis, iatrogenic, paraneoplastic - Parkinson's disease - Multiple sclerosis - Amyotrophic lateral sclerosis - Epilepsy - Dementia - Post-traumatic encephalopathy - Myasthenia - Migraine
Psychiatric disorders	- Mood disorders - Schizophrenia and other psychotic disorders - Anxiety disorders - Post-traumatic stress
Functional disorders Persistent somatic symptoms	Functional somatic syndromes: - Fibromyalgia - Chronic fatigue syndrome - Irritable bowel syndrome
Endocrine disorders	- Hypothyroidism - Primary hyperparathyroidism - Adrenal insufficiency

	- Diabetes
Metabolic disorders	- Hemochromatosis - Lead poisoning - Iron deficiency - Severe vitamin D deficiency - Vitamin B12 deficiency - Glycogen storage disease, lipid storage disorder, mitochondrial respiratory chain diseases
Autoimmune diseases	- Systemic diseases • Systemic lupus erythematosus • Sjögren's syndrome • Scleroderma • Polymyalgia rheumatica - Vasculitis: • Horton's disease • Periarteritis nodosa, ANCA-associated vasculitis
Infectious diseases*	- Viral infections: HIV, HCV, HBV, EBV, CMV, Parvovirus B19 - Bacterial infections: brucellosis, syphilis, Whipple's disease, tuberculosis, other septic arthritis
Various diseases	- Cancers - Sleep apnea

*Bacterial infections potentially transmitted by ticks [babesiosis, coxiellosis (Q fever), bartonellosis (*B. henselae*), rickettsiosis, tularemia, Ehrlichiosis, anaplasmosis] are not responsible for chronic symptoms.