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Médecine et maladies infectieuses

Médecine et maladies infectieuses xxx (2019) xxx–xxx

Review

Lyme borreliosis and other tick-borne diseases. Guidelines from the French Scientific Societies (I): prevention, epidemiology, diagnosis

Borréliose de Lyme et autres maladies vectorielles à tiques. Recommandations des sociétés savantes françaises (Argumentaire I) : prévention, épidémiologie, circonstances du diagnostic

J. Figoni [a,b], C. Chirouze [c], Y. Hansmann [d], C. Lemogne [e], V. Hentgen [f], A. Saunier [g], K. Bouiller [c], J.F. Gehanno [h], C. Rabaud [i], S. Perrot [j], E. Caumes [k], C. Eldin [l], T. de Broucker [m], B. Jaulhac [n], F. Roblot [o], J. Toubiana [p], F. Sellal [q], F. Vuillemet [q], C. Sordet [r], B. Fantin [s], G. Lina [t], X. Gocko [u], M. Dieudonné [v], O. Picone [ah], B. Bodaghi [w], J.P. Gangneux [x], B. Degeilh [x], H. Partouche [y,z], C. Lenormand [aa], A. Sotto [ab], A. Raffetin [ac], J.J. Monsuez [ad], C. Michel [ae], N. Boulanger [n], P. Cathebras [af], P. Tattevin [ag,*], endorsed by scientific societies [l]

[a] *Santé Publique France, 94410 St Maurice, France*
[b] *Maladies infectieuses et tropicales, hôpital Avicenne, 93022 Bobigny, France*
[c] *UMR CNRS 6249, maladies infectieuses et tropicales, université Bourgogne Franche Comté, centre hospitalo-universitaire, 25000 Besançon, France*
[d] *Maladies infectieuses et tropicales, centre hospitalo-universitaire, 67000 Strasbourg, France*
[e] *Inserm U1266, hôpital européen Georges-Pompidou, université Paris Descartes, AP–HP, 75015 Paris, France*
[f] *Centre hospitalier, 78000 Versailles, France*
[g] *Médecine interne et maladies infectieuses, centre hospitalier, 24750 Périgueux, France*
[h] *Médecine du travail, centre hospitalo-universitaire, 76000 Rouen, France*
[i] *Maladies infectieuses et tropicales, centre hospitalo-universitaire, 54100 Nancy, France*
[j] *Centre d'étude et de traitement de la douleur, hôpital Cochin, 75014 Paris, France*
[k] *Maladies infectieuses et tropicales, hôpital La Pitié-Salpêtrière, 75013 Paris, France*
[l] *Maladies infectieuses et tropicales, IHU Méditerranée Infection, centre hospitalo-universitaire Timone, 13000 Marseille, France*
[m] *Neurologie, hôpital Delafontaine, 93200 Saint-Denis, France*
[n] *Laboratoire de bactériologie et CNR des Borrelia, faculté de médecine et centre hospitalo-universitaire, 67000 Strasbourg, France*
[o] *Inserm U1070, maladies infectieuses et tropicales, centre hospitalo-universitaire, 86000 Poitiers, France*
[p] *Service de pédiatrie générale et maladies infectieuses, hôpital Necker – Enfants Malades, AP–HP, 75014 Paris, France*
[q] *Département de neurologie, hôpitaux Civil, 68000 Colmar, France*
[r] *Rhumatologie, centre hospitalo-universitaire, 67000 Strasbourg, France*
[s] *Inserm UMR 1137 IAME, médecine interne, hôpital Beaujon, université Paris Diderot, 92110 Clichy, France*
[t] *Microbiologie, centre hospitalo-universitaire, 69000 Lyon, France*
[u] *Département de médecine générale, faculté de médecine, 42000 Saint-Étienne, France*
[v] *Centre Max Weber, CNRS, université Lyon 2, 69000 Lyon, France*
[w] *Ophtalmologie, hôpital La Pitié-Salpêtrière, 75013 Paris, France*
[x] *UMR_S 1085, Inserm-EHESP, laboratoire de parasitologie-mycologie, Irset université Rennes1, centre hospitalo-universitaire, 35000 Rennes, France*

* Corresponding author.
E-mail address: pierre.tattevin@chu-rennes.fr (P. Tattevin).

[l] Société française de dermatologie (SFD), Société française de rhumatologie (SFR), Fédération française de neurologie (FFN), Société française de neurologie (SFN), Collège national des généralistes enseignants (CNGE), Collège de la médecine générale (CMG), Société nationale française de médecine interne (SNFMI), Société française de microbiologie (SFM), Collège national des professionnels en psychiatrie - Collège national pour la qualité des soins en psychiatrie (CNPP-CNQSP), Association française de psychiatrie biologique et de neuropsychopharmacologie (AFPBN), Société de psychologie medicale et de psychiatrie de liaison de langue française (SPMPLLF), Société française de médecine du travail (SFMT), Société française de cardiologie (SFC), Société française de pédiatrie (SPD), Groupe de pathologies infectieuses pédiatriques (GPIP), Société française de rhumatologie et médecine interne pédiatrique (SOFREMIP), Société française d'ophtalmologie (SFO), Société française de mycologie médicale (SFMM), Société française de parasitologie (SFP), Collège des universitaires de maladies infectieuses et tropicales (CMIT), Collège national des gynécologues et obstétriciens français (CNGOF), Société française d'étude et de traitement de la douleur (SFETD), Société de pathologie infectieuse de langue française (SPILF).

https://doi.org/10.1016/j.medmal.2019.04.381

[y] Cabinet de médecine générale, 93400 Saint-Ouen, France
[z] Département de médecine générale, faculté de médecine, université Paris Descartes, 75006 Paris, France
[aa] Dermatologie, hôpitaux universitaires de Strasbourg et faculté de médecine, université de Strasbourg, 67000 Strasbourg, France
[ab] Maladies infectieuses et tropicales, centre hospitalo-universitaire, 30000 Nîmes, France
[ac] Maladies infectieuses et tropicales, centre hospitalier intercommunal, 94190 Villeneuve-St-Georges, France
[ad] Cardiologie, hôpital René Muret, 93270 Sevran, France
[ae] Médecine générale, Strasbourg, 67000 France
[af] Médecine interne, hôpital Nord, centre hospitalo-universitaire, 42000 Saint-Étienne, France
[ag] Service des maladies infectieuses et réanimation médicale, hôpital Pontchaillou, CHU Pontchaillou, 35033 Rennes cedex, France
[ah] Maternité Louis-Mourier, 92700 Colombes, France

Received 15 March 2019; accepted 9 April 2019

Abstract

Lyme borreliosis is transmitted en France by the tick *Ixodes ricinus*, endemic in metropolitan France. In the absence of vaccine licensed for use in humans, primary prevention mostly relies on mechanical protection (clothes covering most parts of the body) that may be completed by chemical protection (repulsives). Secondary prevention relies on early detection of ticks after exposure, and mechanical extraction. There is currently no situation in France when prophylactic antibiotics would be recommended. The incidence of Lyme borreliosis in France, estimated through a network of general practitioners (*réseau Sentinelles*), and nationwide coding system for hospital stays, has not significantly changed between 2009 and 2017, with a mean incidence estimated at 53 cases/100,000 inhabitants/year, leading to 1.3 hospital admission/100,000 inhabitants/year. Other tick-borne diseases are much more seldom in France: tick-borne encephalitis (around 20 cases/year), spotted-fever rickettsiosis (primarily mediterranean spotted fever, around 10 cases/year), tularemia (50–100 cases/year, of which 20% are transmitted by ticks), human granulocytic anaplasmosis (< 10 cases/year), and babesiosis (< 5 cases/year). The main circumstances of diagnosis for Lyme borreliosis are cutaneous manifestations (primarily erythema migrans, much more rarely borrelial lymphocytoma and atrophic chronic acrodermatitis), neurological (< 15% of cases, mostly meningoradiculitis and cranial nerve palsy, especially facial nerve) and rheumatologic (mostly knee monoarthritis, with recurrences). Cardiac and ophtalmologic manifestations are very rarely encountered.

Keywords: Lyme borreliosis; Prevention; Ticks; France; Erythema migrans; Arthritis; Neuroborreliosis

Résumé

La borréliose de Lyme est transmise en France par la tique *Ixodes ricinus*, présente sur tout le territoire métropolitain. En l'absence de vaccin, la prévention primaire repose sur les mesures de protection mécanique (vêtements couvrants), éventuellement complétées par la protection chimique (répulsifs). La prévention secondaire repose sur le repérage précoce des tiques après exposition et leur extraction mécanique. Il n'existe aucune situation justifiant une antibioprophylaxie post-piqûre de tiques en France. L'incidence de la borréliose de Lyme, estimée à travers le réseau Sentinelles et les codages des séjours hospitaliers, a été stable en France entre 2009 et 2017, avec une moyenne de 53 cas/100 000 habitants/an, à l'origine d'1,3 hospitalisation/100 000 habitants/an. Les autres maladies transmises par les tiques sont beaucoup plus rares en France : encéphalite à tiques (environ 20 cas/an), rickettsioses du groupe 'boutonneux' (fièvre boutonneuse méditerranéenne, environ 10 cas/an), tularémie (50 à 100 cas/an, dont 20 % transmis par des tiques), anaplasmose granulocytaire humaine (< 10 cas/an) et babésiose (< 5 cas/an). Les principaux points d'appel pour une borréliose de Lyme sont les manifestations cutanées (érythème migrant principalement, beaucoup plus rarement lymphocytome borrélien et acrodermatite chronique atrophiante), neurologiques (< 15 % des cas, essentiellement méningoradiculite et atteinte d'un ou plusieurs nerf(s) crânien(s), surtout le nerf facial) et articulaires (principalement monoarthrite récidivante du genou). Les manifestations cardiaques et ophtalmologiques sont exceptionnelles.

Mots clés : Borréliose de Lyme ; Prévention ; Tiques ; France ; Érythème migrant ; Arthrite ; Neuroborréliose

1. Prevention

1.1. Ecology of ticks

Ticks are Acari and are divided into two families: hard ticks known as Ixodidae, and soft ticks known as Argasidae (Table 1). Soft ticks usually bite at night and their blood meal is of a short duration (just a few minutes). They do not transmit infectious agents to humans, but they may cause anaphylactic shocks [1]. The most infectious hard ticks to humans are those of the *Ixodes, Dermacentor*, and *Rhipicephalus* genera. *Ixodes ricinus* and *Dermacentor* ticks are reported in all regions of

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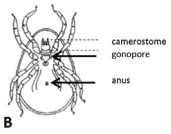
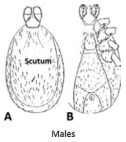
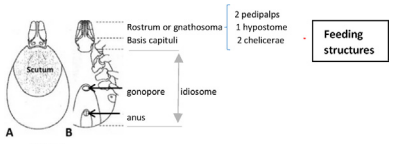
Table 1
Characteristics of ticks.
Caractéristiques des tiques.

	Soft ticks: Argasidae	Hard ticks: Ixodidae
	Feeding structures located on the stomach (camerostome); neither scutum nor scutellum   	Feeding structures located on the sub-terminal part of the body: hypostome and two chelicerae; scutum  
Bite and blood meal	Rather at night; several short blood meals	During the day; a single and long blood meal (several days)
Habitat	Endophilic ticks (grotto, burrows, nests, etc.)	Endophilic ticks – houses *(Rhipicephalus sanguineus)* Vegetation (*Ixodes* sp., *Dermacentor* sp.)
Geographical distribution	Argas: found in pigeons (all French regions) Ornithodoros: rarely reported in France	*Ixodes ricinus*: humid and forest areas, rarely reported in the Mediterranean region (too dry) *Dermacentor*: bites from adult female ticks only, all French regions *Rhipicephalus sanguineus*: dog ticks; doghouses, outside walls of houses, most regions of France Higher biting activity in the south of France
Infectious and non-infectious risk	Non-infectious to humans Risk of an anaphylactic shock via sensitization to the tick's saliva	*Ixodes ricinus*: *Borrelia burgdorferi sensu lato, Borrelia miyamotoi*, *Anaplasma phagocytophilum*, TBE virus, *Babesia* spp., *Rickettsia helvetica, Francisella tularensis, Candidatus* Neoehrlichia mikurensis. *Dermacentor*: *Rickettsia slovaca, Rickettsia raoulti* (TIBOLA), *Rickettsia sibirica* subspecies *mongolitimonae, Francisella tularensis* *Rhipicephalus*: *Rickettsia conorii* (Mediterranean spotted fever) Other risks specifically associated with the saliva of *Ixodes* ticks: ascending tick paralysis, cross-allergy to red meat
Main genera	 ***Argas***  ***Ornithodoros***	*Ixodes, Dermacentor, Rhipicephalus, Hyalomma, Haemaphysalis, Amblyomma* (imported)  ***Rhipicephalus***  ***Haemaphysalis***  ***Dermacentor***  ***Ixodes***  ***Hyalomma***

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metropolitan France, while *Rhipicephalus* ticks are less common.

Ixodes ticks are able to climb on vegetation (up to 1.50-meter high) to find hosts to feed on. They then come back down to rehydrate on the ground. *Ixodes* ticks are highly susceptible to desiccation. They usually bite during the day and their blood meal is of a long duration (several days) [2]. *Dermacentor* ticks usually bite dogs and ungulate animals such as sheep. They may also bite humans, mostly on the scalp. *Rhipicephalus sanguineus* is predominantly observed in warm weather regions with mild winters [2].

In 2016 a quarter of the French metropolitan population reported having been bitten by a tick at least once in their life. Anyone can be exposed to tick bites when partaking in outdoor activities in forests or in the countryside, in urban parks, or private gardens with dense vegetation. Loose ticks found on domestic dogs and cats after outdoor activities also pose a risk to humans [3]. Adult *Dermacentor* and *Ixodes* ticks are present on vegetation because nymphs and larvae are found in animals' burrows. *Rhipicephalus* are endophilic ticks. They are found in doghouses as these ticks are mostly observed in dogs, but they can also be found outside walls of houses or even inside houses. Few tick bites are reported in French overseas territories.

1.2. Personal protection measures against vectors

1.2.1. Primary prevention

Ixodes ticks are the most predominant ticks in our environment. They are active from March to October in continental climate regions and all year round in oceanic climate regions. *Dermacentor* ticks show the same pattern of activity. *Rhipicephalus* ticks are more pathogenic to humans in warm countries [4].

1.2.1.1. Physical protection measures. The best prevention measure relies on wearing full protective clothing. Long trousers should be tucked into the socks – or even gaiters – and long-sleeve shirts are recommended. Light-colored clothing is recommended to facilitate tick detection (grade AE) [5]. Young children should cover their head with a hat. They are indeed at higher risk of being bitten by questing ticks because of their size and types of activity (grade AE).

1.2.1.2. Chemical protection measures. Repellents are known to disrupt the olfactory system of ticks. They prevent ticks from detecting hosts, but they cannot kill the ticks [6]. Repellents should only be used as an additional protection to physical protection measures for occasional exposures, because of the lack of tolerability data with long-term repeated exposures (grade B). Repellents should not be used in pregnant women and children aged below 24 months as the benefit-risk ratio has not been assessed in these populations (grade AE). The recommended repellent molecules are DEET (the only molecule with a marketing authorization in France), IR35/35, KBR 3023, PMDRBO (synthetic active ingredient of eucalyptus citriodora). The following instructions should be followed:

- repellents should be applied to uncovered areas of skin (no efficacy if applied underneath clothing);
- specified age limits and application interval should be strictly observed;
- repellents should not be applied at the same time as sunscreen (grade B) [7].

Essential oils, extracted from plants (lavender, lemongrass, etc.) and highly volatile, are not recommended because of their short repellent action (< 1 hour) (grade AE). Several compounds may act as photosensitizing, irritating, or carcinogenic agents. The efficacy of repellent wristbands has not been proven and their use is therefore not recommended (grade AE). Clothing may be impregnated with pyrethrin-containing repellents (grade AE). However, their tolerability in cases of prolonged use has never been assessed and 0.5% of the applied dose is absorbed by the skin [8].

1.2.1.3. Vaccine protection. No vaccine is currently available against Lyme borreliosis for humans. The tick-borne encephalitis vaccine is recommended when visiting rural or wooded areas in endemic regions from spring to autumn.

1.2.2. Secondary prevention

Secondary prevention includes all measures recommended after a tick bite. Such measures should be adopted even when primary prevention measures have been implemented (grade AE).

People returning from high-risk areas should meticulously check their body for ticks (grade AE) [9], mainly warm and humid body parts (popliteal space, groin and axillary areas, elbow crease, umbilicus), the scalp, and the ears, especially in young children. Bites of *Dermacentor* ticks are usually localized at the base of the scalp, and those of *Rhipicephalus* ticks are localized on lower limbs and skin folds. Taking a shower can provide the opportunity to check one's body more thoroughly. The size of the ticks varies depending on the stages of development (Fig. 1). As ticks grow bigger while blood-feeding on hosts, the body check should be repeated on the day following exposure (grade AE).

The following measures should be adopted in cases of tick detection (grade AE) [9]:

- mechanical extraction of the tick should be performed as soon as possible using a tick remover or thin tweezers: viruses are transmitted right from the start of the blood meal and bacteria or parasites are transmitted within 24 hours. When the feeding structures of the tick cannot be removed, they may safely be left in the skin as the infectious agents are located in the salivary glands, which are part of the tick's body which has been removed. Feeding structures left in the skin usually form a self-limiting granuloma. Ticks should not be removed with fingers or using products such as ether, oil, or nail polish. An inflammation may be observed around the tick bite, due to a reaction to the tick's saliva (Fig. 2). Unlike erythema migrans,

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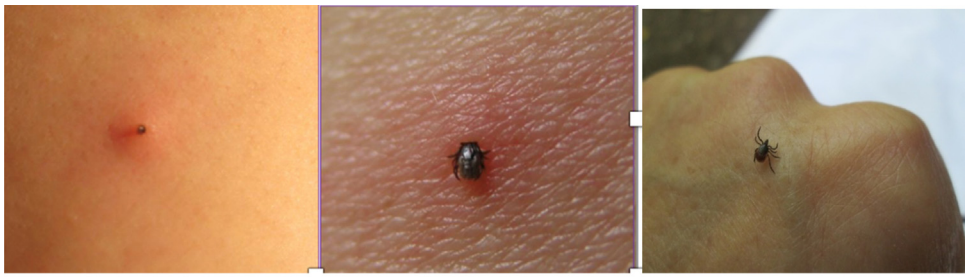

Fig. 1. Stages of development of *Ixodes ricinus.* 1.a: larva; 1.b: nymph; 1.c: adult female tick.
Les différentes stases d'Ixodes ricinus.
N. Boulanger.

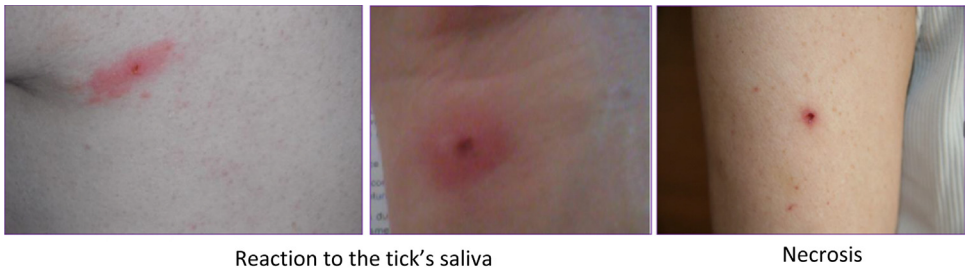

Fig. 2. Examples of cutaneous inflammatory reaction after a tick bite. Reaction to the tick's saliva. Necrosis.
Exemples de réaction inflammatoire cutanée après piqûre de tique.
N. Boulanger.

the inflammation is not extensive and resolves within 48 to 72 hours;
- the skin should be disinfected at the biting site using antiseptics, after tick removal;
- hand washing with soap is recommended;
- a photo of the tick should be taken, and the date and place of the bite should be written down. The photo may then be presented to a physician or pharmacist for tick identification;
- the skin area around the bite should be checked during the four weeks following the bite, to detect signs and symptoms of erythema migrans which would indicate Lyme borreliosis [10], or to detect a black spot. Medical advice should in that case be sought and the recent tick bite should be mentioned to the physician.

The risk of developing Lyme borreliosis after a tick bite is < 5%, even in high-endemicity areas and following prolonged attachment of the tick [11]. Consequently, after a tick bite sustained in France:

- serodiagnosis [12] or a self-performed test is not recommended (grade A);
- performing tests on the extracted tick to look for infectious agents is not recommended (grade A);
- initiating an antibiotic therapy is not recommended, irrespective of the patient's age, of the attachment duration, and of the stage of development of the extracted tick (grade B).

1.3. Collective prevention measures

Tick-borne diseases are zoonoses. Humans are accidental hosts. They are bitten when visiting the ecosystem of ticks [13]. Collective prevention measures are aimed at preventing tick bites by controlling their ecosystem in areas of human activities [9].

1.3.1. Controlling the tick habitat

Reducing the number of ticks may be achieved by cutting grass in green spaces and in areas surrounding houses, and by preserving the forest ecosystems (e.g., avoiding leaving dead branches or wood where rodents live as they act as reservoirs for ticks and some pathogens). Spraying of acaricides is performed in the United States, but it is not allowed in France for environmental reasons.

1.3.2. Protection measures against wild animals

Deer are the main hosts of adult *Ixodes* ticks, and thus contribute to maintaining populations of ticks in the ecosystems [14]. Building fences to keep wild animals at bay reduces the presence of ticks in human activity areas.

1.3.3. Prevention of tick bites sustained via domestic animals

Only loose ticks can be transmitted to humans by domestic animals [3]. The animal's fur should be groomed following outdoor activities or acaricide veterinary treatments should be used (grade AE). Removed ticks should be discarded.

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2. Epidemiology of tick-borne diseases in France

The epidemiology of tick-borne diseases in France is closely related with the ecology of ticks and with their geographical distribution. A surveillance network for Lyme borreliosis has been implemented in France, involving various stakeholders. The surveillance of tick-borne diseases other than Lyme borreliosis is carried out by national reference centers (French acronym CNR, *Centre National de Référence*).

2.1. Lyme borreliosis

The causative agents of Lyme borreliosis in Europe are *Borrelia burgdorferi* sensu stricto, *Borrelia garinii,* and *Borrelia afzelii*. *Borrelia burgdorferi* sensu stricto is predominant in the United States. In France the surveillance is based on:

- a network of family physicians (Sentinel network; Inserm/Sorbonne University, Santé publique France), also involved in the surveillance of other diseases. Family physicians officially report the Lyme borreliosis cases that they diagnose. The same family physicians are part of this network every year and the network thus generates reliable data for trends;
- data from the French hospital discharge database (French acronym PMSI, *Programme de Médicalisation des Systèmes d'Information*) allowing for the surveillance of disseminated Lyme borreliosis requiring hospital admission.

The mean annual incidence of Lyme borreliosis estimated by the Sentinel network in metropolitan France was 53/100,000 inhabitants between 2009 and 2017 (all presentations – 95% of erythema migrans and 5% of early or late disseminated Lyme borreliosis). The peak incidence was observed in 2016 with 84/100,000 inhabitants. One cannot confirm or deny an upward trend in France. The PMSI analysis reveals an incidence of 1.3 hospitalizations/100,000 inhabitants per year over the 2005–2017 period in metropolitan France. Half of these hospitalizations were for neurological presentations. The hospitalization incidence ranged from 1.1/100,000 inhabitants in 2005 to 1.5/100,000 inhabitants in 2011 and 2017, without any significant trend observed. The mean hospitalization rate for Lyme neuroborreliosis between 2005 and 2017 was 0.7/100,000 inhabitants per year. Most patients are diagnosed or hospitalized between March and November, with a peak in July for presentations diagnosed in community settings and between July and September for hospitalizations [15].

Lyme borreliosis is observed in all regions of metropolitan France. Alsace, Lorraine, and Limousin are the most affected regions, while the Mediterranean region has the lowest incidence rates, irrespective of the data source (Fig. 3). Lyme borreliosis has never been reported in French overseas territories as the *Ixodes* vectors do not thrive in these climatic conditions. Lyme borreliosis is most frequently reported in people aged over 60 years, but children below 15 years of age are more frequently hospitalized for Lyme neuroborreliosis. The rare cases of death reported in the global literature are due to cardiac or neurological presentations. A recent Danish study demonstrated that the long-term survival of patients presenting with Lyme neuroborreliosis was not different than that of the general population [16].

Neighboring countries to France have a similar surveillance system (Sentinel network) and report similar estimates with an annual incidence of erythema migrans of 89/100,000 inhabitants in Belgium in 2017 and 113/100,000 inhabitants in Switzerland in 2014 (66/100,000 in France in 2017). Lyme borreliosis is a notifiable disease in nine regions of Germany, with a mean incidence of 33/100,000 inhabitants between 2013 and 2017 [17]. This incidence might be underestimated considering the seroprevalence (9.4% between 2008 and 2011 among adults of the general population in Germany) [18].

Outdoor workers are known to be at risk of Lyme borreliosis through occupational hazard, but literature data is scarce on the proportion attributed to occupational exposure. High seroprevalence rates are reported in forest rangers: 14.1% in the north-east of France [19], 15.2% in the Île-de-France region (Paris area) [20], 21.6% in Belgium, 22% in Poland [21,22], and 28% in the Netherlands [23]. The seroprevalence reported in the control group of the latter study was 5% (administrative staff members, $P < 0.01$). However, the incidence of symptomatic Lyme borreliosis in occupational settings is poorly documented and probably underestimated [24]. Lyme borreliosis is mentioned in two lists of occupational diseases applicable in France (list 19 of the general scheme and list 5bis of the agricultural scheme), where it is defined by clinical signs and symptoms and confirmed by serological tests. In 2015, nine occupational disease cases were reported in list 19 (leptospirosis and Lyme borreliosis cases) and 39 occupational disease cases were reported in List 5bis (only Lyme borreliosis cases).

2.2. Other tick-borne diseases

The incidence of the other tick-borne diseases is much lower: in 2003 in a population at high risk such as forest rangers living in the north-east of France, seroprevalence rates were 5.7% for *Francisella tularensis*, 2.3% for tick-borne encephalitis virus, 1.7% for *Anaplasma phagocytophilum*, 0.1% for *Babesia divergens,* and 2.5% for *Babesia microti* (versus 14.1% for *Borrelia burgdorferi*) [19].

The tick-borne encephalitis (TBE) virus may also be transmitted by *Ixodes* ticks. TBE is endemic in several countries adjacent to France such as Switzerland, some regions of Germany, and in most of the Eastern countries. The incidence of TBE in France remains low, with less than 20 cases reported per year (mainly in the Alsace region). An increase in the incidence of TBE was observed in 2016 and new TBE virus circulation areas were documented, mainly in the Alps [25].

Tick-borne rickettsioses of the spotted fever group are rarely observed in France. They are mainly transmitted by *Rhipicephalus* and *Dermacentor* ticks. The most common rickettsiosis is caused by *Rickettsia conorii*, the causative agent of Mediterranean spotted fever. It is transmitted by dog ticks (*Rhipicephalus sanguineus)* and is observed in the Mediterranean region between spring and summer. Approximately 10 cases per year are diagnosed. Scalp eschar associated with neck

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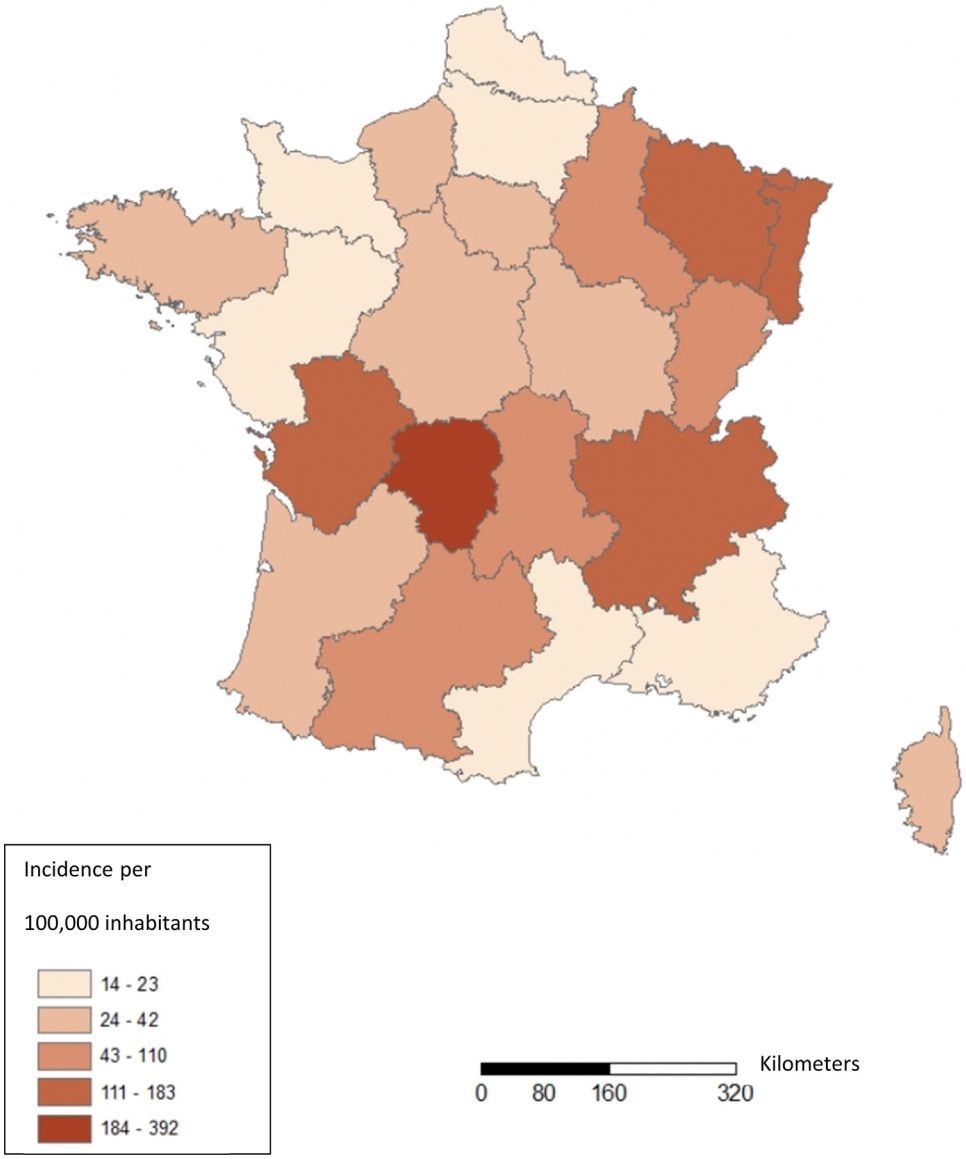

Fig. 3. Estimated incidence of Lyme borreliosis by region, 2013–2017, metropolitan France.
Estimation de l'incidence de la Borréliose de Lyme par région, 2013–2017, France métropolitaine.
Santé publique France, based on data from the Sentinel network, 2019.

lymphadenopathy after tick bite (SENLAT), also known as tick-borne lymphadenitis (TIBOLA), is mainly caused by *Rickettsia slovaca*. Lymphangitis-associated rickettsiosis (LAR) is due to *Rickettsia sibirica* subspecies *mongolotimonae.* Both of these rickettsioses are transmitted by *Dermacentor* ticks, which are present in the whole French territory and responsible for less than 10 cases per year in France.

Tularemia is a notifiable disease, mainly transmitted by direct skin contact with infected animals (mainly jackrabbits), contaminated plants, soil, or materials. Between 50 and 100 cases of tularemia are reported every year in France, including 20% after a tick bite.

Babesiosis is a parasitic disease transmitted by *Ixodes ricinus* ticks in Europe. The disease is frequently observed in animals (mainly bovines), but very rarely in humans [26]. Approximately 15 cases caused by *Babesia divergens* have been reported in France.

Human granulocytic anaplasmosis (HGA) is also transmitted by *Ixodes ricinus* ticks. HGA is usually diagnosed in Eastern France and is responsible for approximately 10 cases per year [27].

Borrelia miyamotoi is present in *Ixodes ricinus* ticks in France, but no human case has ever been reported. This might be due to poor vector competence. Very rare cases have been reported in Europe, while many cases are reported in Russia where the bacterium is transmitted by highly competent vectors, i.e., *Ixodes persulcatus* ticks.

Only 18 cases of *Candidatus* Neoehrlichia mikurensis symptomatic infections have been reported in Europe [28], including 16 cases in immunocompromised patients. No case has ever

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Table 2
Main differential diagnoses for cutaneous presentations of Lyme borreliosis.
Principaux diagnostics différentiels des formes cutanées de la borréliose de Lyme.

Differential diagnosis	Distinctive features
Erythema migrans	
Reaction to the arthropod's bite	Immediate lesion after the bite, pruritus, no progressive extension
Urticaria	Extension within less than 12–24 hours, pruritus, edema
Granuloma annulare	Lesions may be infiltrated, irregular with slow extension, and specific histological aspect
Fixed pigmented erythema	Drug intake, no extension of the lesions
Scleroderma	Skin atrophy (mild presentations), induration (typical presentations), no regular extension, specific histological aspect
Dermatophytosis	Vesicular borders, squamous or scaly, severe pruritus, positive scale mycological sample
Borrelial lymphocytoma	
Pseudo non-borrelial lymphocytoma	Specific context (drug intake, tattoo, etc.), negative *Borrelia* serology, no decrease with treatment
Sarcoidosis	Lupoid aspect at vitropression, specific histological aspect
Primary cutaneous B cell lymphoma	Specific histological aspect (caution is required as borrelial lymphocytoma may sometimes mimic the histological features of a lymphoma)
Acrodermatitis chronica atrophicans	
Chronic venous insufficiency (stasis dermatitis)	Abnormal vascular check-up, recurrent inflammatory flares with pruritus and eczema, ocher dermatitis, no atrophy
Acrosyndromes (acrocyanosis, erythromelalgia)	Bilateral, often paroxysmal and room temperature-dependent, no atrophy
Complex regional pain syndrome	Trauma or surgery, vasomotor disorders, hyperhidrosis, no atrophy

been diagnosed in France, but the bacterium has been detected in *Ixodes* ticks.

Crimean-Congo hemorrhagic fever (CCHF) is transmitted by *Hyalomma marginatum* ticks, reported on the Mediterranean coast. The virus has never been detected in ticks in France. However, cases have been reported in Greece, Bulgaria, Turkey, and Spain (three cases in 2016 and 2018, including one nosocomial transmission) [29]. Transmission of *Coxiella burnetii*, the causative agent of Q fever, by tick bites, has never been documented. Only three cases of *Bartonella henselae* bartonellosis probably transmitted by ticks have been reported in France. The infections led to acute SENLAT [30]. Despite the potential presence of these infectious agents in ticks reported in France [31], their vector competence in transmitting diseases to humans has never been proven [32]. Tick bites sustained when traveling abroad may expose to other diseases requiring a specialist consultation.

3. When should Lyme borreliosis or other tick-borne diseases be suspected?

All clinical situations should benefit from a comprehensive management. The context, environment, patient's lifestyle habits, and clinical history should be taken into consideration. The management should be based on a patient-centered strategy and the patient's point of view should always be considered [33]. The holistic patient-centered strategy should be associated with meticulous clinical judgment from physicians, who should consider the expected prevalence of the disease based on the patient's signs [34]. We suggest using a strategy based on symptoms suggestive of Lyme borreliosis (Table 2). Other symptoms, rarely reported in Lyme borreliosis, should first lead physicians to suspect other diagnoses.

3.1. Cutaneous signs suggestive of Lyme borreliosis

Cutaneous signs are the most common manifestations of Lyme borreliosis. Three types of lesions are usually observed and are associated with differential diagnoses (Table 2).

3.1.1. Single erythema migrans (localized stage) or multiple erythema migrans (early disseminated stage [35])

Erythema migrans should be suspected when the following type of macule is observed: pinkish to reddish color, oval-shaped, central clearing (not in all cases), regular growth (often >5 cm at the time of diagnosis), centrifugal extension, without pruritus, and mark at the site of the tick bite (not in all cases) (grade B). Several erythematous macules, especially in children, should lead physicians to suspect multiple erythema migrans, although rarely reported in France. Single and multiple erythema migrans may be associated with flu-like symptoms [36]. No laboratory investigation is required as serological tests are usually negative and histological findings are poorly specific [32] (grade B).

3.1.2. Borrelial lymphocytoma [37]

Borrelial lymphocytoma (early disseminated stage) should be suspected when the following types of plaques or nodules are observed: single lesion, very slow-growing, varying color (from pink to bright red, dark purple, or reddish-brown), asymptomatic (or with barely any pruritus), unusual localizations (ear lobe in children [38], breast areola in adults, exceptionally localized on the face, thorax, or limbs) (grade B). General symptoms may be observed. A skin biopsy may be useful (dense lymphocytic infiltrate of the dermis) to rule out differential diagnoses (grade AE). *Borrelia* serological test results are usually positive.

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Table 3
Investigations for the differential diagnosis of Lyme neuroborreliosis.
Examens complémentaires utiles pour le diagnostic différentiel des neuroborrélioses.

Clinical situation	Investigations	Signs indicative of Lyme neuroborreliosis	Differential diagnosis
Meningoradiculitis	Medullary MRI Lumbar puncture	Radicular or leptomeningeal contrast enhancement	Nerve root compression, meningoradiculitis caused by other bacteria
Polyneuropathy	Electromyography	Cannot be length-dependent distal symmetrical polyneuropathy	Other more common causes of polyneuropathy
Acute or subacute encephalitis	Brain MRI Lumbar puncture	CSF/serum antibody index	HSV encephalitis, tick-borne encephalitis
Cerebrovascular disorders	Brain MRI or CT scan	Lacunar infarct	Atherothrombotic or cardioembolic stroke
Chronic encephalopathy	Cognitive assessment Brain MRI Lumbar puncture		Degenerative dementia and related disorders

MRI: magnetic resonance imaging; CSF: cerebrospinal fluid; HSV: herpes simplex virus; CT: computed tomography. European criteria for the diagnosis of Lyme neuroborreliosis: Lyme neuroborreliosis-compatible symptoms otherwise unexplained; CSF pleocytosis; antibody index indicative of anti-*Borrelia* antibody intrathecal synthesis.

3.1.3. Acrodermatitis chronica atrophicans [39,40]

Acrodermatitis chronica atrophicans (ACA) (late disseminated stage) should be suspected in adults aged above 50 years presenting with a macule or a plaque on a limb segment, of varying color (dark red to purplish-blue), more visible where bones are located closer to the skin, with progression from an initial edematous stage to atrophy (abnormally thin, wrinkled, and shiny at the skin surface) (grade AE). Infiltrated areas (fibrous nodules or periarticular fibrous lines) and pain triggered by light touch (allodynia) are suggestive of ACA. Sclerosis areas (induration) may be observed [41]. *Borrelia* serological test results are always positive, with high IgG levels. A skin biopsy may contribute to establishing the diagnosis (collagen abnormalities, telangiectasia, interstitial infiltrate with plasma cells) [42].

3.2. Neurological manifestations suggestive of Lyme neuroborreliosis

Neurological impairment is the second most common manifestation in France (6.5%–15% of Lyme borreliosis cases), following skin manifestations. Neurological impairment is observed at the early disseminated stage (<6 months) in more than 90% of cases [43] (grade B). Lyme neuroborreliosis cases reported in Europe are caused by *Borrelia garinii* in approximately two-thirds of cases and by *Borrelia afzelii* in one-quarter of cases.

3.2.1. When should Lyme neuroborreliosis be suspected and how should it be confirmed?

Any neurological manifestation following untreated erythema migrans or after a tick bite should lead physicians to suspect Lyme neuroborreliosis (grade AE). The diagnosis is based on two-tier serology and on cerebrospinal fluid (CSF) antibody index [44] (Table 3) (grade B). The lumbar puncture usually documents lymphocytic meningitis. The intrathecal synthesis index is based on the ratio between CSF/serum levels for specific antibodies, and CSF/serum total IgG. Serological test and antibody index are always positive in patients with late Lyme neuroborreliosis. These tests are essential for establishing diagnosis [45] (grade B). The sensitivity of *Borrelia* PCR in CSF is too low (10%-30%) to recommend this test after six weeks of symptoms [46] (grade B).

3.2.2. Clinical manifestations suggestive of Lyme neuroborreliosis

Lyme neuroborreliosis mainly presents as meningoradiculitis and cranial nerve palsy, mainly of the facial nerve [43,47,48]. These manifestations should lead physicians to suspect Lyme neuroborreliosis, irrespective of the context (grade A):

- meningoradiculitis (Bannwarth syndrome) accounts for 67% to 85% of Lyme neuroborreliosis cases in Europe. Meningoradiculitis causes atypical, radicular, intractable pain, leading to insomnia, that may extend beyond radicular areas. They are often localized at the thoracic level. Meningoradiculitis in the body part affected by the tick bite or erythema migrans lesion is suggestive of Lyme neuroborreliosis. Sensory deficits and motor deficits, potentially delayed, may be observed. Facial palsy and headaches are common [43,45]. Lymphocytic meningitis with positive antibody index is highly suggestive of Lyme neuroborreliosis [43]. Pain may persist for several months if left untreated. Appropriate antibiotic therapy is usually rapidly effective (within a few days) on pain relief;
- peripheral facial palsy is reported in more than 36% of Lyme neuroborreliosis cases in Europe. Isolated impairment of another cranial nerve (oculomotor or optic nerve) is much

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less common. Facial palsy is bilateral and asynchronous in one-third of cases. Facial palsy is mostly reported in children; Lyme borreliosis accounts for 30% of facial palsies in endemic areas in this population. *Borrelia* serological testing is then systematically indicated in this setting. The need for lumbar puncture should be discussed when peripheral facial palsy is observed in children in endemic areas, especially if a tick bite occurred over the previous weeks (grade AE). Isolated facial palsy in adults (without any headache nor any associated sign) should also lead to *Borrelia* serological testing. However, it should not delay the initiation of corticosteroid therapy as its efficacy in Bell's palsy has been proven if initiated early on (grade AE). A lumbar puncture should be performed when the Elisa serological test for Lyme borreliosis is positive (grade AE).

3.2.3. Clinical manifestations compatible with Lyme neuroborreliosis, although less common

Clinical meningitis, acute myelitis, and encephalitis are much less frequently observed [48], but they should lead to Lyme neuroborreliosis suspicion in the presence of risk factors for exposure (grade B). Late manifestations of Lyme neuroborreliosis diagnosed more than six months after disease onset account for 1% to 9% of cases.

Isolated meningitis (5% of Lyme neuroborreliosis cases) presents as headaches and nausea, more rarely with meningitis signs. The CSF analysis reveals lymphocytic meningitis, high CSF protein level, normal CSF glucose level, and may reveal oligoclonal IgG bands.

Acute transverse myelitis (< 5% of Lyme neuroborreliosis cases), affecting several segments, are predominantly observed in the neck.

Acute or subacute encephalitis accounts for 6% of hospitalized Lyme neuroborreliosis cases [49].

Cerebrovascular impairment (< 1% of Lyme neuroborreliosis cases) may be observed at the early or late disseminated stage.

Asymmetric sensory axonal polyneuropathy (late disseminated stage) is associated with ACA. Length-dependent distal symmetrical polyneuropathy is not suggestive of Lyme neuroborreliosis [43].

Chronic encephalomyelitis (> 6-month duration) related to meningovascular CNS involvement has rarely been reported. Signs and symptoms are similar to those of chronic meningitis with headaches, weight loss, neurosensory disorders, and spastic-ataxic gait [50].

Lyme neuroborreliosis is a very rare cause of cognitive disorders and dementia, even in high-prevalence regions for Lyme disease [51]. Lyme neuroborreliosis should however be investigated in the absence of other etiologies, as it can be cured (grade AE).

3.3. Rheumatologic manifestations suggestive of Lyme borreliosis

3.3.1. Joint symptoms

Arthralgia is a common sign of Lyme borreliosis (50%–70%) at the early stages. The typical joint manifestation of disseminated Lyme borreliosis is monoarthritis (affecting the knee in 85% of cases), and more rarely oligoarthritis. Typical Lyme monoarthritis is a subacute arthritis; patients can still move the affected joint, and are able to walk (Figs. 4 and 5). Onset occurs from a few weeks to two years after the bite. In the absence of an adequate antibiotic therapy, the joint disorder progresses through successive flares interspersed with remission periods [52–54]. Ten per cent of cases progress towards a chronic presentation. Flares of arthritis persist for several weeks or months, with decreasing frequency over time. Patients are usually cured within five years, even when no antibiotic therapy is administered. Half of arthritis patients in Northern America first present with erythema migrans, while the proportion is only 20% in European patients. These patients do not necessarily recall any tick bite (< 25% of cases).

3.3.2. Muscular symptoms

Muscular symptoms are clinically pleomorphic, localized, and associated with other manifestations of Lyme borreliosis (neurological, articular, ACA). Chronic myalgia has been reported, associated with DNA detection in muscle samples (PCR), but its mechanism has not been described [5]. The existence of Lyme myositis seems highly unlikely.

3.3.3. Atypical presentations

Many atypical joint manifestations have been reported (polyarthritis, axial and/or peripheral enthesopathy), with low level of scientific evidence: the diagnosis was only based on serological testing, and very rarely documented by the presence of *Borrelia burgdorferi* in the joints or tendons.

3.4. Cardiac manifestations suggestive of Lyme borreliosis

Cardiac involvement is a complication of Lyme borreliosis in 0.3%–4% of cases, but this prevalence may reach 10% in the United States [55,56] (Table 4). The histopathologically-documented prevalence reported in animal models is higher than the clinically-documented prevalence observed in humans [56,57]. Onset of cardiac manifestations after erythema migrans varies (median, 21 days; range 7 days–7 months) [56]. The delay between erythema migrant and cardiac involvement may be asymptomatic and may also present as the first manifestation of Lyme borreliosis [58]. Outcome is favorable in 90% of cases, but conduction disorders may require temporary cardiac pacing in 30% of cases – more rarely long-term cardiac pacing – especially in elderly patients.

3.4.1. Conduction disorders

The most common cardiac manifestations are nodal atrioventricular (AV) blocks (44% of cases), type 3 AV blocks (49%), type 2 AV blocks (16%), and type 1 AV blocks (12%) [55] (grade B). Subnodal AV blocks and left or right fascicular blocks are less frequently reported. Sinoatrial blocks and arrhythmia, atrial fibrillation, supraventricular or ventricular tachycardia have been reported [55,59,60].

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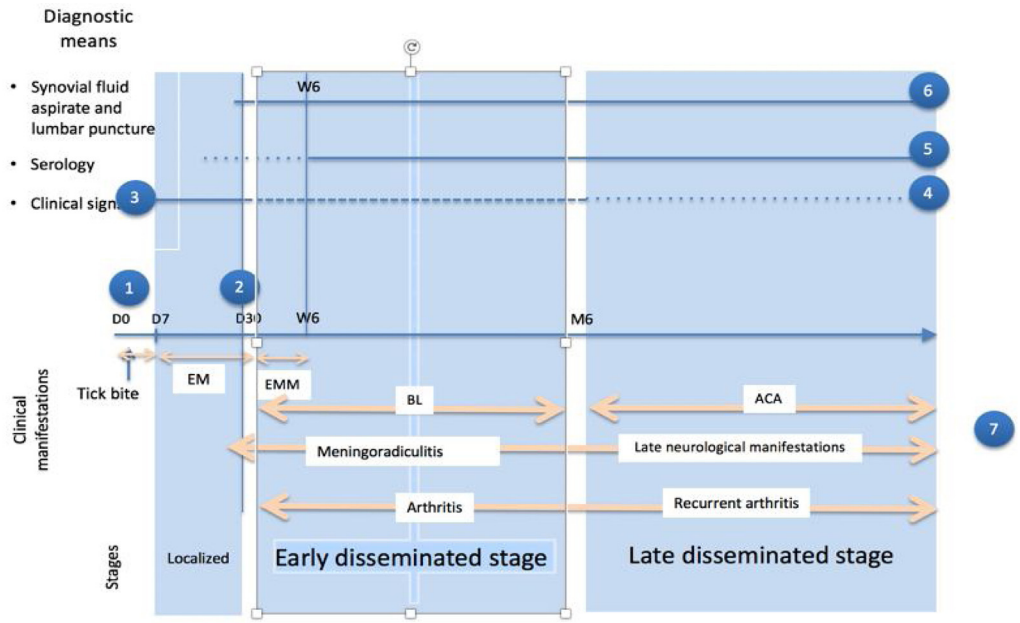

1 Duration of the tick bite may last from 4 to 7 days depending on the tick's stage of development

2 Erythema migrans may still be observed at meningoradiculitis onset

3 Diagnosis at the early stage only relies on clinical signs

4 Clinical signs are less specific at disseminated stages, especially at late disseminated stages.

5 Serology may be negative at the early stages, but its sensitivity is satisfactory from the sixth week on. For late stages, serology has excellent negative predicative value.

6 *Borrelia* identification in synovial fluid or CSF and meningitis associated with intrathecal synthesis of specific antibodies ascertain Lyme borreliosis diagnosis.

7 50% to 70% of disseminated presentations are not preceded by erythema migrans and patients do not necessarily recall or notice the tick bite.

Fig. 4. Natural history of Lyme borreliosis and diagnostic tests. EM: erythema migrans, EMM: multiple erythema migrans, BL: Borrelial lymphocytoma, ACA: acrodermatitis chronica atrophicans.
Histoire de la maladie et tests diagnostiques.

3.4.2. *Myocardial involvement*

Myocarditis, left ventricular dysfunction, or cardiac failure are very rarely associated with Lyme borreliosis (grade B). Lyme borreliosis may be suspected in the absence of any other plausible cause. The estimated prevalence of myocarditis is 0.4%–4% of Lyme borreliosis cases in Europe [59]. Left ventricular dysfunction is usually mild to moderate, as assessed by echocardiography. It can be associated with electrocardiogram (ECG) repolarization abnormalities and elevated biomarker levels (troponin, BNP, NT-proBNP) [59].

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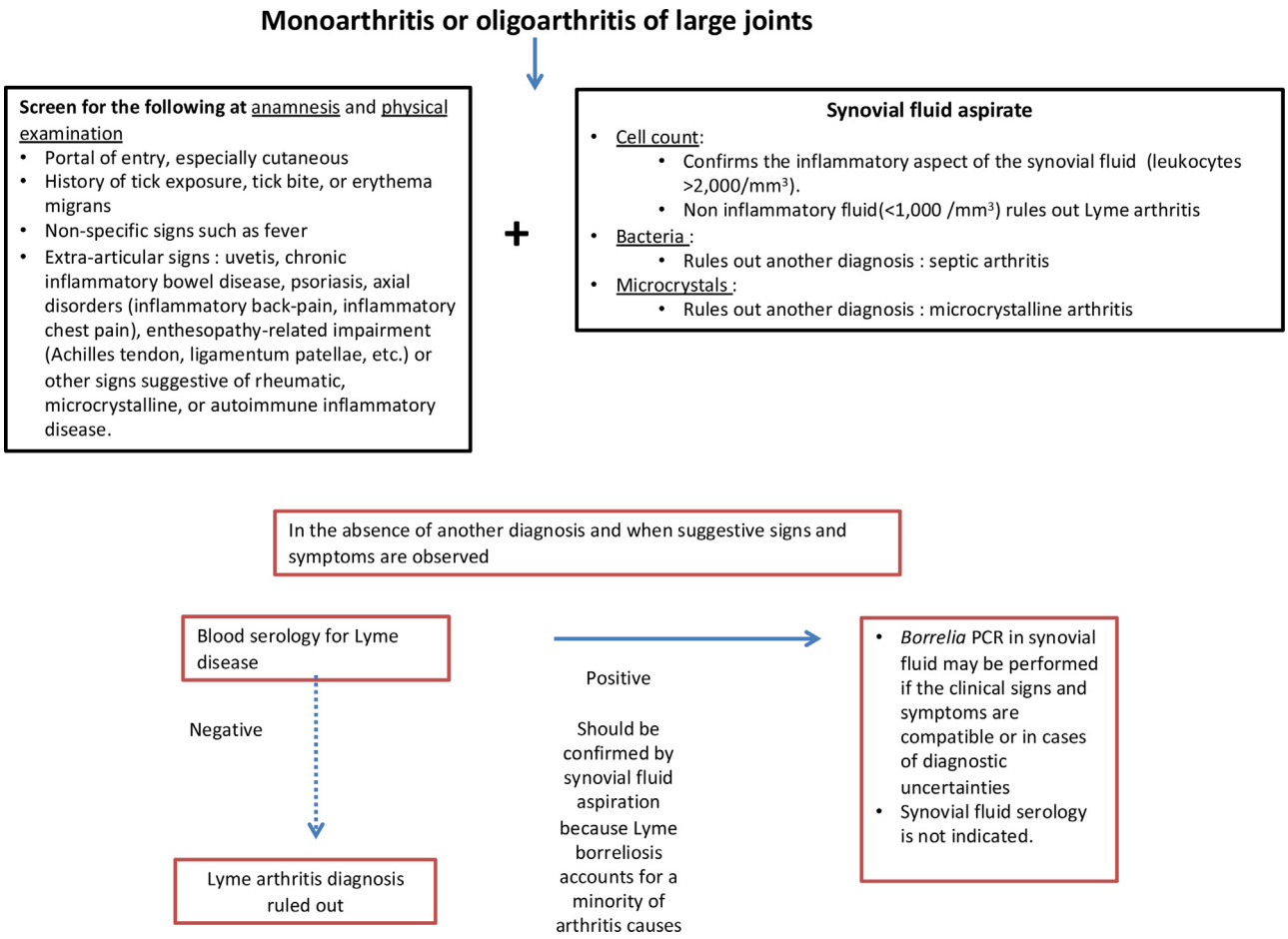

Fig. 5. Diagnostic strategy for joint manifestations of Lyme borreliosis.
Algorithme diagnostique pour les manifestations articulaires des borrélioses.

Table 4
Cardiac assessment of Lyme borreliosis: when and how should it be performed?
Bilan cardiaque d'une borréliose de Lyme : quand, comment ?

Recommendation	Grade	Evidence level
Cardiac symptoms (chest pain, dyspnea, palpitation, syncope) are screened at anamnesis for patients with Lyme borreliosis	I	B
When cardiac symptoms are observed, symptom-guided cardiac assessment should be performed	I	B
ECG changes or elevated troponin levels require the advice and follow-up of a cardiologist	I	C
Holter monitoring is performed in patients with first- or second-degree atrioventricular blocks or with supraventricular or ventricular arrythmia	I	C
Patients with second- or third-degree atrioventricular blocks, PR interval ≥ 300 ms, or left ventricular dysfunction should be hospitalized with ECG monitoring	I	C
Indication for temporary or long-term cardiac pacing depends on the severity of the atrioventricular block and outcome on antibiotic treatment	I	C

ECG: electrocardiogram. Cardiac assessment should either be considered because of the patient's symptoms (palpitation, syncope, chest pain, dyspnea) or to detect a subclinical disease.

3.4.3. Pericarditis

The prevalence of pericarditis in Lyme carditis is 23% [61]. It should be suspected in cases of pericarditis of unknown etiology (grade AE).

3.5. Ophthalmologic manifestations of Lyme borreliosis

Ophthalmologic manifestations of Lyme borreliosis are poorly known. As most reports are based on serological findings,

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imputability of ophthalmologic manifestations to Lyme borreliosis cannot be ascertained. Very few reports documented *Borrelia burgdorferi* tropism for the eye with positive PCR in ocular tissue samples or with ophthalmologic manifestations (uveitis) concomitant to Lyme neuroborreliosis confirmed by CSF analysis [62–64].

3.6. Management strategies for other atypical manifestations of Lyme borreliosis

Lyme borreliosis should not be systematically suspected in patients presenting with common signs and symptoms such as fatigue, headaches, or cramps. Patients consulting for such symptoms, including those living in a high-prevalence area, are more likely to have another disease than Lyme borreliosis. Lyme borreliosis diagnosis is often suspected in excess, especially when only tick-borne diseases are considered, as it can affect the physician's judgment. The concept of heuristic anchoring results from this impaired judgment: "a cognitive process where an individual has excessive trust in an initial piece of information (the "anchor"), without reassessing the facts when confronted with new pieces of information". This cognitive bias may lead to maintaining the Lyme borreliosis hypothesis, without reassessing the likelihood of such diagnosis even when diagnostic tests and treatment response should lead physicians to reconsider the initial diagnosis. Interrupting diagnostic workout too early, i.e. without considering all hypotheses, is another cognitive bias [34,65]. These cognitive biases may lead physicians to prescribe pointless tests and treatments.

When a diagnostic hypothesis cannot be confirmed, one should not suspect another less plausible hypothesis such as Lyme borreliosis, unless symptom progression or further examination results call into question the initial hypothesis. Clinical signs and symptoms may sometimes be explained by the presence of several comorbidities. A recent French cohort study reported that 10% of patients consulting for a suspicion of Lyme borreliosis presented with bone and joint pain related to arthritis or scoliosis [66].

3.7. When should another tick-borne disease be suspected?

Other tick-borne diseases cause acute clinical signs and symptoms (Table 5). As these infections are rarely observed in France, the advice of an infectious disease specialist is often required.

3.7.1. Tick-borne encephalitis

TBE virus infection is usually asymptomatic. Evolution of clinical signs of symptomatic TBE is usually divided in two stages following the incubation period (7-14 days; maximum 4 weeks). The first stage combines fever, myalgia, and headaches. Following spontaneous improvement, one-third of patients further develop signs of meningitis and encephalitis approximately one week later (confusion, drowsiness, gait disorders, tremors in the extremities, speech disorders, cerebellar syndrome) (grade B). Myelitis or meningoradiculitis may also be observed.

The diagnosis of TBE relies on lumbar puncture, revealing lymphocytic meningitis. Specific IgM detection in serum or CSF confirms TBE diagnosis (grade B). IgM antibodies usually appear within the first six days of neurological symptoms and may persist up to 10 months. IgG antibodies persist lifelong in serum.

No curative treatment is available. Management relies on a symptomatic treatment. Outcome is favorable in most cases, but 10% of patients present with neurological sequelae. Case fatality ranges from 0.5% to 2%. An effective TBE vaccine is available, but French health authorities only recommend it for people traveling to endemic areas.

3.7.2. Tick-borne rickettsioses

All rickettsioses of the spotted fever group present as a black spot at the site of the tick bite, with onset of clinical signs within one week after the bite (grade B). Patients with Mediterranean spotted fever (*Rickettsia conorii*) present with a black spot associated with fever, headaches, myalgia, and diffuse maculopapular rash (palm of the hand and sole of the foot included). Severe presentations are reported in 5% of cases with organ failures and disseminated intravascular coagulation in elderly patients and/or patients with comorbidities: diabetes, alcoholism, G6PD deficiency.

Rickettsia sibirica mongolotimonae is responsible for similar signs and symptoms, combining fever, headaches, myalgia, black spot, and maculopapular rash. Painful lymphangitis signs (from bedsore to satellite adenopathy) are indicative of lymphangitis-associated Rickettsia. Patients with TIBOLA (mainly *Rickettsia slovaca* and *Rickettsia raoulti*) present with a black spot on the scalp, headaches, low fever, and painful cervical adenopathy.

The diagnosis of rickettsioses is based on serological testing that needs to be repeated three weeks later (grade B). The *Rickettsia* PCR may be performed on a skin biopsy or on a black spot swab (grade B), CNR for *Rickettsia*: https://www.mediterranee-infection.com/conduite-a-tenir-lors-dune-piqûre-de-tique/.

The first-line treatment of tick-borne rickettsioses is based on doxycycline 200 mg/day for adults and 4 mg/kg/day for children. Treatment should be continued up to 48 hours after apyrexia. Priority is given to azithromycin (10 mg/kg/day for three days) for children below 8 years of age and pregnant women. An empirical treatment is recommended in patients presenting with a black spot, fever, and skin rash because of the potential severity of Mediterranean spotted fever (grade B). The prognosis of tick-borne rickettsioses is favorable, except for severe presentations of Mediterranean spotted fever. Cervical adenopathy and asthenia observed in patients with TIBOLA may persist for several weeks.

3.7.3. Tularemia

Symptoms onset occurs 1 to 14 days following inoculation. The ulceroglandular presentation is the most common with initial fever and diffuse myalgia, followed by ulcer formation at the inoculation site associated with satellite adenopathy. Other presentations, such as oculoglandular, oropharyngeal, or pulmonary presentations, are due to other transmission modes. The

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Table 5
Management of patients presenting with symptoms within four weeks of a tick bite sustained in France.
Stratégie de prise en charge en cas de symptômes débutant dans les 4 semaines suivant une piqûre de tique en France.

Clinical presentation	Pathologies to consider	Exposure/clinical features	Biological parameters	Diagnostic strategy	Treatment to consider
Fever + signs of meningitis OR encephalitis	TBE	Eastern France, French region of Savoie (people traveling to endemic areas)	Lymphocytic meningitis	IgM and IgG serology in serum and CSF	Symptomatic
Fever + lymphadenopathy + black spot	Tularemia			PCR/culture of pus from a lymph node; black spot swab; serology	ciprofloxacin or doxycycline
	Senlat/Tibola	Localization on the scalp		PCR on black spot swab, lymph node aspiration PCR, serology	doxycycline
	Lymphangitis-associated Rickettsia	Lymphangitis signs ± maculopapular rash			doxycycline
Fever + splenomegaly	Babesiosis			Blood smear, PCR	Combination of an antibiotic and an antiparasitic treatment[a]
Fever + maculopapular rash	Rickettsioses	Mediterranean region, localization on the palms of the hands and on the soles of the feet	Cytopenia	Lymph node aspiration PCR, serology	doxycycline
	Anaplasmosis		Cytopenia + lymphocyte activation + cytolytic hepatitis	Blood PCR, serology	doxycycline
Skin ulcer with or without fever	Mediterranean spotted fever	Mediterranean region	Cytopenia	PCR on black spot swab, lymph node aspiration PCR, serology	doxycycline
	Tularemia			PCR/culture of pus from a lymph node; black spot swab; serology	ciprofloxacin OR doxycycline
	TIBOLA, SENLAT	Scalp		PCR on black spot swab, lymph node aspiration PCR, serology	doxycycline

All infections transmitted by ticks can present as isolated fever. Less specific symptoms are often associated with fever: myalgia and digestive disorders. They may be observed in most febrile patients and should not be considered in that context as signs suggestive of a more specific cause. Fatigue/asthenia is often observed; however, when no other objective sign is observed, fatigue is not suggestive of a tick-borne disease.

[a] Treatment requiring advice from an infectious disease specialist; TBE: tick-borne encephalitis, CSF: cerebrospinal fluid, PCR: polymerase chain reaction, SENLAT: scalp eschar associated with neck lymphadenopathy after tick bite; TIBOLA: tick-borne lymphadenitis.

diagnosis relies on serological testing by indirect immunofluorescence or microscopic agglutination test, and antibodies usually appear within two or three weeks. *Francisella tularensis* detection by culture or PCR may be performed (blood cultures, lymph node aspiration). Samples should be sent to the CNR for *Francisella* for confirmation. Classified as a highly pathogenic microorganism, the handling of *Francisella* sp. should be performed in a biosafety laboratory. Treatment of tularemia is based on doxycycline 200 mg/day or ciprofloxacin 500 mg twice daily for 14 days. Combination with an aminoglycoside may be discussed for severe presentations or unfavorable outcome.

3.7.4. Babesiosis

Babesiosis is most often asymptomatic in immunocompetent individuals. Onset of symptomatic presentations occurs one to four weeks after the tick bite with high fever, headaches, and myalgia (grade AE). More severe signs and symptoms may be observed, especially in asplenic patients (hemolysis, myelosuppression, hepatopathy, jaundice, hemoglobinuria, disseminated intravascular coagulation). The diagnosis of babesiosis may be established by blood smear examination by an experienced biologist, but PCR testing is more sensitive in cases of low parasitemia (grade AE). As serology remains positive for many

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years, it is pointless when no indicative symptoms are observed: a positive serology would then be indicative of a former resolved infection. Treatment of babesiosis is species-dependent and requires the advice of a specialist. It is based on the combination of clindamycin and quinine, or azithromycin and atovaquone. The use of artemisinin has not been assessed in the treatment of babesiosis and is therefore not recommended.

3.7.5. Human granulocytic anaplasmosis

Signs and symptoms of human granulocytic anaplasmosis combines fever, arthromyalgia, headaches, chills, thrombocytopenia, leukopenia, and cytolytic hepatitis within two weeks after a tick bite (grade B). Human granulocytic anaplasmosis is usually self-limiting within 30 days, but severe manifestations have been reported in the United States with multiple organ failure in patients presenting with neoplasia. The diagnosis of human granulocytic anaplasmosis is based on specific PCR testing in blood samples, collected at the febrile stage of the infection and then sent to the *Borrelia* CNR for analysis. Serological testing by indirect immunofluorescence can be performed for diagnostic purposes in cases of seroconversion (antibody level increase by at least four-fold) or a level >1/256, once fever has subsided. Serological testing should be repeated three weeks after symptom onset. Treatment is based on doxycycline 200 mg/day in adults or 4 mg/kg/day in children aged over 8 years, for 7 days (or rifampicin 300 mg twice daily). No treatment failure has ever been documented.

3.7.6. Other tick-borne diseases at risk of emergence in France

Crimean-Congo hemorrhagic fever is a viral hemorrhagic fever with symptom onset three to seven days after the tick bite with fever and myalgia, conjunctivitis, and digestive symptoms. These signs and symptoms are usually observed for three days and may be followed by an hemorrhagic stage of variable severity for two to three days with thrombocytopenia, leukopenia, and cytolytic hepatitis. Human-to-human transmission is possible, including to healthcare professionals if basic infection control measures are not implemented.

Borrelia miyamotoi relapsing fever is observed two weeks after a bite by *Ixodes* tick and combines fever, asthenia, headaches, and myalgia. Fever may relapse at nine-day intervals on average (grade B). Neurological, ocular, and hematological complications are very rarely observed and mostly impact severely immunocompromised patients. The infection may lead to complications in pregnant women. The reference treatment is doxycycline.

Candidatus Neoehrlichia mikurensis symptomatic infections have been reported in immunocompromised patients (hematology or rheumatology patients receiving immunosuppressive drugs). *Candidatus* Neoehrlichia mikurensis symptomatic infection is associated with myalgia and arthralgia (grade B). The diagnosis is based on blood PCR testing (CNR for *Borrelia* or *Rickettsia*) as the bacterium cannot be cultured. No serological testing is currently available. Reported cases were treated with doxycycline, with disappearance of symptoms after five days of treatment on average [28].

Disclosure of interest

C. Lemogne contributed to a scientific committee for Lundbeck, was granted funding from Lundbeck and Otsuka Pharmaceutical for congresses or research activities, and received payment from Daiichi-Sankyo, Janssen-Cilag, Lundbeck, and Servier for specific contribution or work. V. Hentgen contributed to scientific committees for Novartis pharma, SOBI, and ABBVE, was granted funding from Novartis pharma for congresses or research activities, and received payment from Novartis pharma for specific contribution. A. Saunier was granted funding from Novartis, Gilead, ViiV Healthcare, Genzyme, and LFB Médicaments for congresses or research activities, and received payment from Novartis and Ceformed for specific contribution. K. Bouiller received payment from Ceformed for providing training courses. P. Cathebras was granted funding from Sanofi-Genzyme, GSK, Novartis, and LFB for congresses, and received payment from MSD, ADEPUL, and MG-Form for specific contribution. C. Eldin was granted funding from Sanofi-Genzyme, GSK, Novartis, and LFB for congresses, and received payment from MSD, ADEPUL, and MG-Form for specific contribution. B. Jaulhac acted as one-off expert speaker for the ANSM, HAS, and ECDC. He contributed to developing the patent for a vaccine against Lyme disease in dogs (N° 1551182). B. Fantin contributed to a scientific committee for Novartis and was granted funding for research/congress purposes from Eumedica. B. Bodaghi contributed to a scientific committee for AbbVie and Allergan, and was granted funding from Santen, AbbVie, Allergan, Bayer, and Thea for congresses or research activities. J.-P. Gangneux contributed to a scientific committee for Pfizer and MSD, and was granted funding from Pfizer and MSD for congresses or research activities. H. Partouche was granted funding from Pfizer for a congress and research activity. F. Sellal was granted funding from Biogen-Idec, Roche, TEVA, Sanofi, and Elivie for congresses or research activities, and received payment from Novartis-Pharma, Sanofi, Lundbeck, Eisai, and TEVA. C. Chirouze was granted funding from Astellas, Gilead, ViiV Healthcare, MSD, and Janssen for congresses or research activities, and received payment from BMS for specific contribution. A. Raffetin was granted funding from MSD and Elivie for congresses or research activities. C. Rabaud contributed to scientific committees for MSD, GSK, Pfizer, AstraZeneca, Janssen, Astellas, Gilead, and ViiV Healthcare, and was granted funding from Mylan, Astellas, Janssen, MSD, and Gilead for congresses or research activities. F. Roblot contributed to scientific committees for Janssen, was granted funding from Astellas, Eumedica, Novartis, Pfizer, Sanofi, and MSD for congresses or research activities, and received payment from GSK, MSD, and Astellas for one-off contributions. P. Tattevin contributed to scientific committees for Gilead, Astellas, Coreviome, MSD, Mylan, and Pfizer, was granted funding from Astellas, bioMérieux, Gilead, Pfizer, and MSD for congresses or research activities, and received payment from Mylan, MSD,

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Pfizer, bioMérieux, Gilead, and Astellas for one-off contributions.

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Médecine et maladies infectieuses xxx (2019) xxx–xxx

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Review

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

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

B. Jaulhac[a], A. Saunier[b], E. Caumes[c], K. Bouiller[d], J.F. Gehanno[e], C. Rabaud[f], S. Perrot[g], C. Eldin[h], T. de Broucker[i], F. Roblot[j], J. Toubiana[k], F. Sellal[l], F. Vuillemet[l], C. Sordet[m], B. Fantin[n], G. Lina[o], C. Sobas[o], X. Gocko[p], J. Figoni[q,r], C. Chirouze[d], Y. Hansmann[s], V. Hentgen[t], P. Cathebras[u], M. Dieudonné[v], O. Picone[ag], B. Bodaghi[w], J.P. Gangneux[x], B. Degeilh[x], H. Partouche[y], C. Lenormand[z], A. Sotto[aa], A. Raffetin[ab], J.J. Monsuez[ac], C. Michel[ad], N. Boulanger[n], C. Lemogne[ae], P. Tattevin[af,*], endorsed by scientific societies[1]

[a] *Laboratoire de bactériologie et cnr des Borrelia, faculté de médecine et centre hospitalo-universitaire, 67000 Strasbourg, France*
[b] *Médecine interne et maladies infectieuses, centre hospitalier, 24750 Périgueux, France*
[c] *Maladies infectieuses et tropicales, hôpital La Pitié-Salpêtrière, 75013 Paris, France*
[d] *Maladies infectieuses et tropicales, centre hospitalo-universitaire, UMR CNRS 6249 Université Bourgogne Franche Comté, 25000 Besançon, France*
[e] *Médecine du travail, centre hospitalo-universitaire, 76000 Rouen, France*
[f] *Maladies infectieuses et tropicales, centre hospitalo-universitaire, 54100 Nancy, France*
[g] *Centre d'étude et de traitement de la douleur, hôpital Cochin, 75014 Paris, France*
[h] *Maladies infectieuses et tropicales, ihu méditerranée infection, centre hospitalo-universitaire Timone, 13000 Marseille, France*
[i] *Neurologie, hôpital Delafontaine, 92300 Saint-Denis, France*
[j] *Maladies infectieuses et tropicales, centre hospitalo-universitaire, inserm U1070, 86000 Poitiers, France*
[k] *Service de pédiatrie générale et maladies infectieuses, hôpital Necker–Enfants Malades, AP–HP, 75014 Paris, France*
[l] *Département de neurologie, hôpitaux civil, 68000 Colmar, France*
[m] *Rhumatologie, centre hospitalo-universitaire, 67000 Strasbourg, France*
[n] *Médecine interne, hôpital Beaujon, université Paris Diderot, Inserm UMR 1137 IAME, 92110 Clichy, France*
[o] *Microbiologie, centre hospitalo-universitaire, 69000 Lyon, France*
[p] *Département de médecine générale, faculté de médecine, 42000 Saint-Etienne, France*
[q] *Maladies Infectieuses et tropicales, hôpital Avicenne, 93022 Bobigny, France*
[r] *Santé publique France, 94410 St Maurice, France*
[s] *Maladies infectieuses et tropicales, centre hospitalo-universitaire, 67000 Strasbourg, France*
[t] *Pédiatrie, centre hospitalier, 78000 Versailles, France*
[u] *Médecine interne, hôpital Nord, centre hospitalo-universitaire, 42000 Saint-Etienne, France*

* Corresponding author at: Service des maladies infectieuses et réanimation Médicale, CHU Pontchaillou, 35033 Rennes cedex, France.
E-mail address: pierre.tattevin@chu-rennes.fr (P. Tattevin).

[1] Société française de dermatologie (SFD), Société française de rhumatologie (SFR), Fédération française de neurologie (FFN), Société française de neurologie(SFN), Collège national des généralistes enseignants (CNGE), Collège de la médecine générale (CMG), Société nationale française de médecine interne (SNFMI),Société française de microbiologie (SFM), Collège national des professionnels en psychiatrie - Collège national pour la qualité des soins en psychiatrie(CNPP-CNQSP), Association française de psychiatrie biologique et de neuropsychopharmacologie (AFPBN), Société de psychologie médicale et de psychiatrie déliaison de langue française (SPMPLLF), Société française de médecine du travail (SFMT), Société française de cardiologie (SFC), Société française de pédiatrie(SPD), Groupe de pathologies infectieuses pédiatriques (GPIP), Société française de rhumatologie et médecine interne pédiatrique (SOFREMIP), Société française d'ophtalmologie (SFO), Société française de mycologie médicale (SFMM), Société française de parasitologie (SFP), Collège des universitaires de maladies infectieuses et tropicales (CMIT), Collège National des Gynécologues et Obstétriciens Français (CNGOF), Société française d'étude et de traitement de la douleur(SFETD), Société de pathologie infectieuse de langue française (SPILF).

https://doi.org/10.1016/j.medmal.2019.05.001
0399-077X/

[v] Centre Max Weber, CNRS, Université Lyon 2, 69000 Lyon, France
[w] Ophtalmologie, hôpital La Pitié-Salpêtrière, 75013 Paris, France
[x] Laboratoire de parasitologie-Mycologie, UMR_S 1085 Irset université Rennes1-Inserm-EHESP, centre hospitalo-universitaire, 35000 Rennes, France
[y] Cabinet de médecine générale, Saint-Ouen, département de médecine Générale, faculté de médecine. université Paris Descartes, 93400 Paris, France
[z] Dermatologie, hôpitaux universitaires de Strasbourg et faculté de médecine, université de Strasbourg, 67000 Strasbourg, France
[aa] Maladies infectieuses et tropicales, centre hospitalo-universitaire, 30000 Nîmes, France
[ab] Maladies infectieuses et tropicales, centre hospitalier intercommunal, 94190 Villeneuve-St-Georges, France
[ac] Cardiologie, hôpital René Muret, 93270 Sevran, France
[ad] Médecine générale, 67000 Strasbourg, France
[ae] Psychiatrie, hôpital européen Georges-Pompidou, AP–HP.5, Inserm U1266; Université Paris Descartes, 75015 Paris, France
[af] Maladies infectieuses et réanimation médicale, hôpital Pontchaillou, centre hospitalo-universitaire, 35033 Rennes, France
[ag] Maternité Louis Mourier, 92700 Colombes, France

ARTICLE INFO

Article history:
Received 30 March 2019
Accepted 7 May 2019
Available online xxx

Keywords:
Lyme borreliosis
Western blot
Neuroborreliosis
Erythema migrans
Persistent somatic symptoms

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.

Mots-clés :
Borréliose de Lyme
Western blot
Neuroborréliose
Érythème migrant
Symptomatologie somatique persistante

RÉSUMÉ

Le sérodiagnostic de borréliose de Lyme repose sur une stratégie en 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.

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 common [2]: seropositivity alone is not sufficient 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

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Table 1
Performance of diagnostic tests (sensitivity/specificity) in European Lyme borreliosis.
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.
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)

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 symptoms onset, the serological test is associated with > 90% sensitivity and specificity [3–5]. For early disseminated manifestations with neurological symptoms within six weeks after the tick bite (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

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reveals IgG targeted against numerous *B. 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-*B. 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 *B. 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 *B. 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)

Regarding *B. burgdorferi* DNA PCR detection, 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 *B. 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 for cutaneous (PCR test on skin biopsy) or joint manifestations (PCR test on synovial fluid or synovial biopsy). 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 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 *B. 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 symptoms 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

Erythema migrans spontaneously resolves without treatment (within a few weeks), but *B. burgdorferi* sensu lato may persist

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Table 3
Treatment of erythema migrans (single or multiple) and of borrelial lymphocytoma.
Traitement de l'érythème migrant, unique ou multiple, et du lymphocytome borrélien.

Antibiotics		Dosing regimen duration	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[a]	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

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

in the skin [24] and new manifestations may occur later on. An antibiotic therapy is therefore required, with documented efficacy, irrespective of symptoms 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) (Table 3).

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 symptoms, 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

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 (Table 3).

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 palsies, and/or peripheral nervous system manifestations. Ceftriaxone or doxycycline are recommended in patients presenting with central nervous system manifestations, 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 may be harmful to patients presenting with facial palsy associated with early Lyme neuroborreliosis [45]. Jarisch-Herxheimer reaction has not been reported in European studies of Lyme neuroborreliosis

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Table 4
Treatment of Lyme neuroborreliosis.
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[a]	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[b]	21 days
IV ceftriaxone	2 g once daily	80 mg/kg once daily (maximum 2 g)	21 days

[a] 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.
[b] Central nervous system impairment = encephalitis, myelitis, vasculitis.

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 symptoms 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). Symptoms 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

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 limited sample size. They are based on long-term follow-up (>12 months) [50,51]. The inclusion criteria for these studies are usually non-specific joint signs associated with positive serology. Some of the patients enrolled may not have active Lyme borreliosis (Table 5).

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 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, and new manifestations in four [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, lead 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 (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).

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

Antibiotics	Adults	Children	Duration
Oral doxycycline[a] 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[a]
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)	

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

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 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 for 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

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 (Table 6).

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 case reports 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 are 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,

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Table 6
Treatment of ophthalmologic manifestations of Lyme borreliosis.
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 (2nd 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

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 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 investigations.

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:

- chronic and incapacitating physical symptoms that cannot be entirely attributed to anatomical lesions;
- 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 accounted for 36% and 56% of diagnoses in 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:

- let the patient tell the "disease history" that led him to suspect he may have Lyme borreliosis;

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Table 7
Possible causes of persistent symptoms after documented or suspected Lyme borreliosis.
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[a]
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

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

- list all arguments developed by the patient in favor of Lyme borreliosis diagnosis;
- assess the patient's conviction related to the Lyme borreliosis diagnosis (the physician may ask the patient to grade this likelihood using percentages);
- 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;
- 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 different treatments.

Physicians should look at investigations already performed before deciding on further investigations. However, biological and radiological investigations 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 (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 controversies. The diagnostic workout 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

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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):

- 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.).
- 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].
- 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.
- 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.
- 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.
- 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.
- Physicians should suggest a positive diagnosis. As there is no consensus on the preferred term, the choice should be based on the term in line 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.
- 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.
- 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.
- 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.

Disclosure of interests

C. Lemogne contributed to a scientific committee for Lundbeck, was granted funding from Lundbeck and Otsuka Pharmaceutical for congresses or research activities, and received payment from Daiichi-Sankyo, Janssen-Cilag, Lundbeck, and Servier for specific contribution or work. V. Hentgen contributed to scientific committees for Novartis pharma, SOBI, and ABBVIE, was granted funding from Novartis pharma for congresses or research activities, and received payment from Novartis pharma for specific contribution. A. Saunier was granted funding from Novartis, Gilead, ViiV Healthcare, Genzyme, and LFB Médicaments for congresses or research activities, and received payment from Novartis and Ceformed for specific contribution. P. Cathebras was granted funding from Sanofi-Genzyme, GSK, Novartis, and LFB for congresses, and received payment from MSD, ADEPUL, and MG-Form for specific contribution. C. Eldin was granted funding from Sanofi-Genzyme, GSK, Novartis, and LFB for congresses, and received payment from MSD, ADEPUL, and MG-Form for specific contribution. B. Jaulhac acted as one-off expert speaker for the ANSM, HAS, and ECDC. He contributed to developing the patent for a vaccine against Lyme disease in dogs (N° 1551182). B. Fantin contributed to a scientific committee for Novartis and was granted funding for congresses or research activities from Eumedica. B. Bodaghi contributed to a scientific committee for AbbVie and Allergan, and was granted funding from Santen, AbbVie, Allergan, Bayer, and Thea for congresses or research activities. J.-P. Gangneux contributed to a scientific committee for Pfizer and MSD, and was granted funding

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from Pfizer and MSD for congresses or research activities. H. Partouche was granted funding from Pfizer for congresses and research activities. F. Sellal was granted funding from Biogen-Idec, Roche, TEVA, Sanofi, and Elivie for congresses or research activities, and received payment from Novartis-Pharma, Sanofi, Lundbeck, Eisai, and TEVA. C. Chirouze was granted funding from Astellas, Gilead, ViiV Helathcare, MSD, and Janssen for congresses or research activities, and received payment from BMS for specific contribution. Thomas de Broucker was granted funding from Novartis Pharma for congresses or research activities, and received payment from Biogen France, Sanofi, Novartis Pharma, and Roche for specific contribution. A. Raffetin was granted funding from MSD and Elivie for congresses or research activities. E. Caumes received payment from Takeda Pharmaceuticals International AG and Zambon for specific contribution. C. Rabaud contributed to scientific committees for MSD, GSK, Pfizer, AstraZeneca, Janssen, Astellas, Gilead, and Viiv Healthcare, and was granted funding from Mylan, Astellas, Janssen, MSD, and Gilead for congresses or research activities. A. Sotto contributed to scientific committees for Sanofi and BioFilm Control, and received payment from Astellas and MSD for congresses. Y. Hansmann was granted funding from Pfizer, Astellas, Jansen, Gilead, and Eumedica for congresses, teaching, or research activities. F. Roblot contributed to scientific committees for Janssen, was granted funding from Astellas, Eumedica, Novartis, Pfizer, Sanofi, and MSD for congresses or research activities, and received payment from GSK, MSD, and Astellas for one-off contributions. P. Tattevin contributed to scientific committees for Gilead, Astellas, Coreviome, MSD, Mylan, and Pfizer, was granted funding from Astellas, BioMérieux, Gilead, Pfizer, and MSD for congresses or research activities, and received payment from Mylan, MSD, Pfizer, BioMérieux, Gilead, and Astellas for one-off contributions. C. Sordet was granted funding from Abbvie, MSD, Pfizer, BMS, Roche-Chugai, Lilly, Mylan, Biogen, for congress, expertise or research activities.

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