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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

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[1] Société française de dermatologie (SFD), Société française de rhumatologie (SFR), Fédération française de neurologie (FFN), Société française de neurologie (SFN), La liste des sociétés savantes a subi quelques modifications: remplacer par la liste ci-jointeCollège 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 obstétriciens et gynécologues (CNOG), Société française d'étude et de traitement de la douleur (SFETD), Société de pathologie infectieuse de langue française (SPILF).

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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.

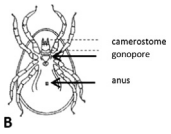
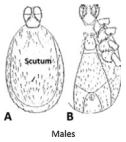
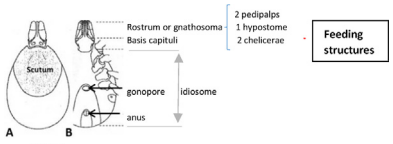
Mots clés : Borréliose de Lyme ; Prévention ; Tiques ; France ; Érythème migrant ; Arthrite ; Neuroborréliose

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

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***

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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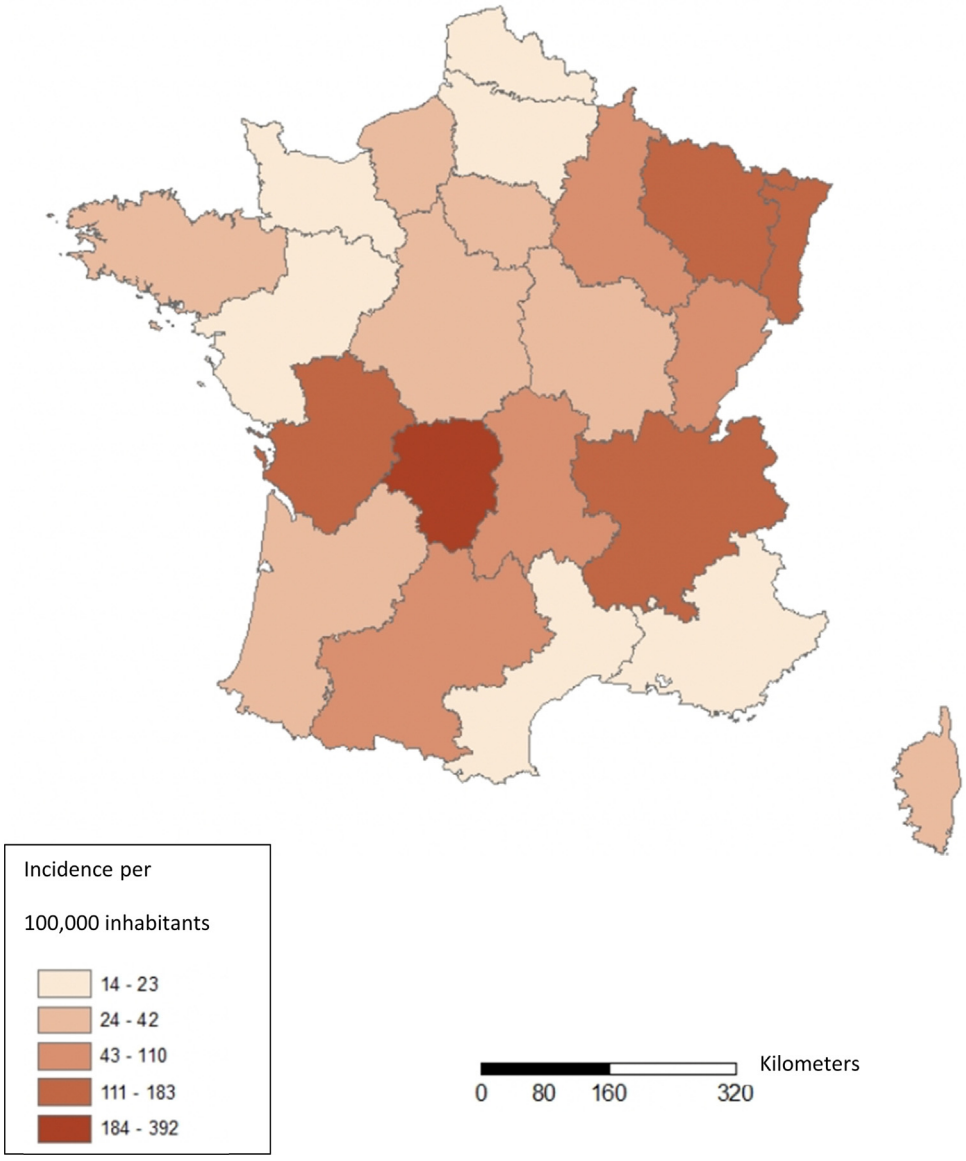

Fig. 3. Estimated incidence of Lyme borreliosis by region, 2013–2017, metropolitan France.
Estimation de l'incidence de la Borréliose de Lyme par région, 2013–2017, France métropolitaine.
Santé publique France, based on data from the Sentinel network, 2019.

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

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 by *Coxiella burnetii* tick bites, the causative agent of Q fever, 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

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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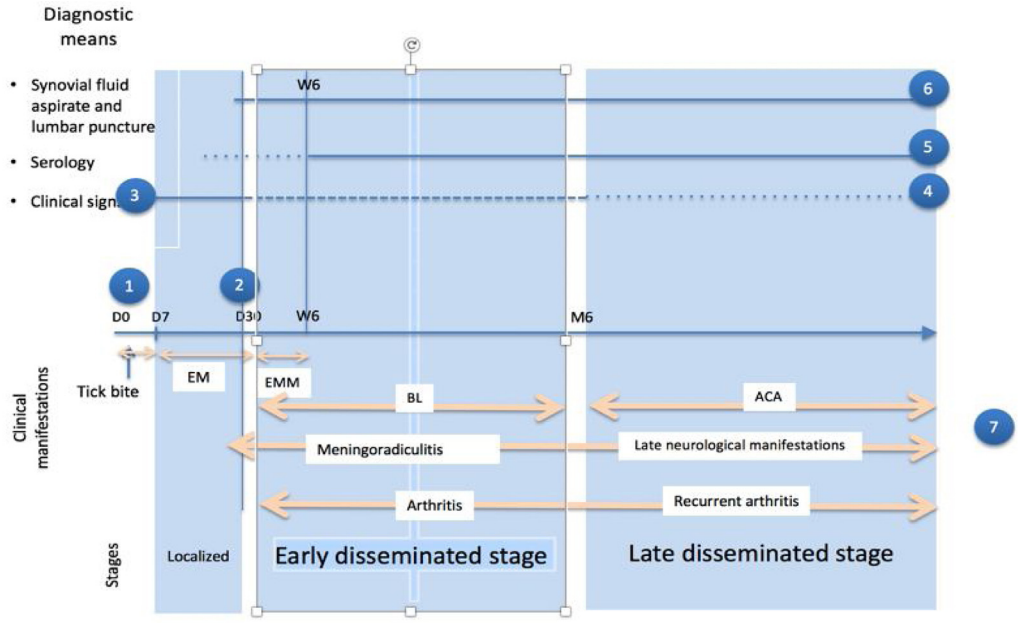

1 Duration of the tick bite may last from 4 to 7 days depending on the tick's stage of development

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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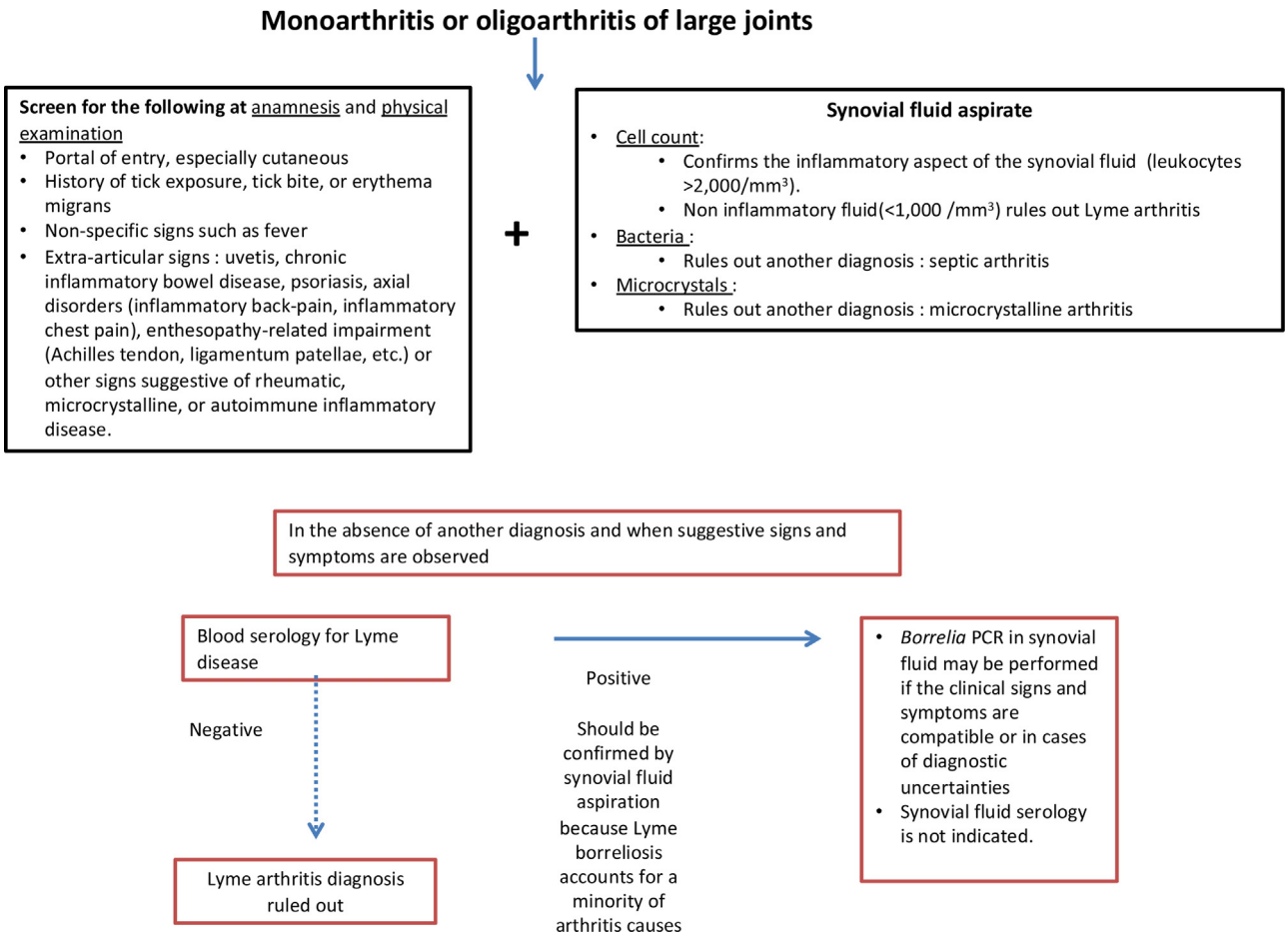

Fig. 5. Diagnostic strategy for joint manifestations of Lyme borreliosis.
Algorithme diagnostique pour les manifestations articulaires des borrélioses.

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,

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 diagno-

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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.

sis 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

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References

[1] Hilger C, Bessot JC, Hutt N, Grigioni F, De Blay F, Pauli G, et al. IgE-mediated anaphylaxis caused by bites of the pigeon tick Argas reflexus: cloning and expression of the major allergen Arg r 1. J Allergy Clin Immunol 2005;115:617–22.
[2] Boulanger N, Boyer P, Talagrand-Reboul E, Hansmann Y. Ticks and tick-borne diseases. Med Mal Infect 2019.
[3] Jones EH, Hinckley AF, Hook SA, Meek JI, Backenson B, Kugeler KJ, et al. Pet ownership increases human risk of encountering ticks. Zoonoses Public Health 2018;65:74–9.
[4] Parola P, Socolovschi C, Jeanjean L, Bitam I, Fournier PE, Sotto A, et al. Warmer weather linked to tick attack and emergence of severe rickettsioses. PLoS Negl Trop Dis 2008;2:e338.
[5] Eisen L, Dolan MC. Evidence for Personal Protective Measures to Reduce Human Contact With Blacklegged Ticks and for Environmentally Based Control Methods to Suppress Host-Seeking Blacklegged Ticks and Reduce Infection with Lyme Disease Spirochetes in Tick Vectors and Rodent Reservoirs. J Med Entomol 2016.
[6] Pages F, Dautel H, Duvallet G, Kahl O, de Gentile L, Boulanger N. Tick repellents for human use: prevention of tick bites and tick-borne diseases. Vector Borne Zoonotic Dis 2014;14:85–93.
[7] Montemarano AD, Gupta RK, Burge JR, Klein K. Insect repellents and the efficacy of sunscreens. Lancet 1997;349:1670–1.
[8] van der Rhee HJ, Farquhar JA, Vermeulen NP. Efficacy and transdermal absorption of permethrin in scabies patients. Acta Derm Venereol 1989;69:170–3.
[9] Due C, Fox W, Medlock JM, Pietzsch M, Logan JG. Tick bite prevention and tick removal. BMJ 2013;347:f7123.
[10] Boulanger N, Lipsker D. [Protection against tick bites]. Parasit Vectors 2015;142:245–51.
[11] Schwameis M, Kundig T, Huber G, von Bidder L, Meinel L, Weisser R, et al. Topical azithromycin for the prevention of Lyme borreliosis: a randomised, placebo-controlled, phase 3 efficacy trial. Lancet Infect Dis 2017;17:322–9.
[12] Stanek G, Wormser GP, Gray J, Strle F. Lyme borreliosis. Lancet 2012;379:461–73.
[13] Kilpatrick AM, Randolph SE. Drivers, dynamics, and control of emerging vector-borne zoonotic diseases. Lancet 2012;380:1946–55.
[14] Kilpatrick HJ, LaBonte AM, Stafford KC. The relationship between deer density, tick abundance, and human cases of Lyme disease in a residential community. J Med Entomol 2014;51:777–84.
[15] Vandenesch A, Turbelin C, Couturier E, Arena C, Jaulhac B, Ferquel E, et al. Incidence and hospitalisation rates of Lyme borreliosis, France, 2004 to 2012. Euro Surveill 2014;19.
[16] Obel N, Dessau RB, Krogfelt KA, Bodilsen J, Andersen NS, Moller JK, et al. Long term survival, health, social functioning, and education in patients with European Lyme neuroborreliosis: nationwide population based cohort study. BMJ 2018;361 [k1998].
[17] Enkelmann J, Bohmer M, Fingerle V, Siffczyk C, Werber D, Littmann M, et al. Incidence of notified Lyme borreliosis in Germany, 2013–2017. Sci Rep 2018;8:14976.
[18] Wilking H, Fingerle V, Klier C, Thamm M, Stark K. Antibodies against Borrelia burgdorferi sensu lato among adults, Germany, 2008–2011. Emerg Infect Dis 2015;21:107–10.
[19] Rigaud E, Jaulhac B, Garcia-Bonnet N, Hunfeld KP, Femenia F, Huet D, et al. Seroprevalence of seven pathogens transmitted by the Ixodes ricinus tick in forestry workers in France. Clin Microbiol Infect 2016;22 [735.e731–739].
[20] Zhioua E, Rodhain F, Binet P, Perez-Eid C. Prevalence of antibodies to Borrelia burgdorferi in forestry workers of Ile de France, France. Eur J Epidemiol 1997;13:959–62.
[21] De Keukeleire M, Robert A, Luyasu V, Kabamba B, Vanwambeke SO. Seroprevalence of Borrelia burgdorferi in Belgian forestry workers and associated risk factors. Parasit Vectors 2018;11:277.
[22] Kiewra D, Szymanowski M, Zalewska G, Dobracka B, Dobracki W, Klakocar J, et al. Seroprevalence of Borrelia burgdorferi in forest workers from inspectorates with different forest types in Lower Silesia, SW Poland: preliminary study. Int J Environ Health Res 2018;28:502–10.
[23] Kuiper H, van Dam AP, Moll van Charante AW, Nauta NP, Dankert J. One year follow-up study to assess the prevalence and incidence of Lyme borreliosis among Dutch forestry workers. Eur J Clin Microbiol Infect Dis 1993;12:413–8.
[24] Piacentino JD, Schwartz BS. Occupational risk of Lyme disease: an epidemiological review. Occup Environ Med 2002;59:75–84.
[25] Velay A, Solis M, Kack-Kack W, Gantner P, Maquart M, Martinot M, et al. A new hot spot for tick-borne encephalitis (TBE): a marked increase of TBE cases in France in 2016. Ticks Tick Borne Dis 2018;9:120–5.
[26] Gorenflot A, Moubri K, Precigout E, Carcy B, Schetters TP. Human babesiosis. Ann Trop Med Parasitol 1998;92:489–501.
[27] Edouard S, Koebel C, Goehringer F, Socolovschi C, Jaulhac B, Raoult D, et al. Emergence of human granulocytic anaplasmosis in France. Ticks Tick Borne Dis 2012;3:403–5.
[28] Portillo A, Santibanez P, Palomar AM, Santibanez S, Oteo JA. 'Candidatus Neoehrlichia mikurensis' in Europe. New Microbes New Infect 2018;22:30–6.
[29] Negredo A, de la Calle-Prieto F, Palencia-Herrejon E, Mora-Rillo M, Astray-Mochales J, Sanchez-Seco MP, et al. Autochthonous Crimean-Congo hemorrhagic fever in Spain. N Engl J Med 2017;377:154–61.
[30] Angelakis E, Pulcini C, Waton J, Imbert P, Socolovschi C, Edouard S, et al. Scalp eschar and neck lymphadenopathy caused by Bartonella henselae after Tick Bite. Clin Infect Dis 2010;50:549–51.
[31] Vayssier-Taussat M, Kazimirova M, Hubalek Z, Hornok S, Farkas R, Cosson JF, et al. Emerging horizons for tick-borne pathogens: from the "one pathogen-one disease" vision to the pathobiome paradigm. Future Microbiol 2015;10:2033–43.
[32] Eldin C, Raffetin A, Bouiller K, Hansmann Y, Roblot F, Raoult D, et al. Review of European and American guidelines for the diagnosis of Lyme borreliosis. Med Mal Infect 2019;49:121–32.
[33] Charles C, Gafni A, Whelan T. Shared decision-making in the medical encounter: what does it mean? (or it takes at least two to tango). Soc Sci Med 1997;44:681–92.
[34] Nendaz M, Charlin B, Leblanc V, Bordage G. Le raisonnement clinique: données issues de la recherche et implications pour l'enseignement. Pedagog Med 2005;6(4):35–54.
[35] Stupica D, Maraspin V, Bogovic P, Ogrinc K, Blagus R, Cerar T, et al. Comparison of Clinical Course and Treatment Outcome for Patients With Early Disseminated or Early Localized Lyme Borreliosis. JAMA Dermatol 2018;154:1050–6.
[36] Strle F, Lusa L, Ruzic-Sabljic E, Maraspin V, Lotric Furlan S, Cimperman J, et al. Clinical characteristics associated with Borrelia burgdorferi sensu lato skin culture results in patients with erythema migrans. PLoS One 2013;8:e82132.
[37] Maraspin V, Nahtigal Klevisar M, Ruzic-Sabljic E, Lusa L, Strle F. Borrelial Lymphocytoma in adult patients. Clin Infect Dis 2016;63:914–21.
[38] Arnez M, Ruzic-Sabljic E. Borrelial Lymphocytoma in children. Pediatr Infect Dis J 2015;34:1319–22.
[39] Brehmer-Andersson E, Hovmark A, Asbrink E. Acrodermatitis chronica atrophicans: histopathologic findings and clinical correlations in 111 cases. Acta Derm Venereol 1998;78:207–13.
[40] Lenormand C, Jaulhac B, Debarbieux S, Dupin N, Granel-Brocard F, Adamski H, et al. Expanding the clinicopathological spectrum of late cutaneous Lyme borreliosis (acrodermatitis chronica atrophicans [ACA]): A prospective study of 20 culture- and/or polymerase chain reaction (PCR)-documented cases. J Am Acad Dermatol 2016;74:685–92.
[41] Zollinger T, Mertz KD, Schmid M, Schmitt A, Pfaltz M, Kempf W. Borrelia in granuloma annulare, morphea and lichen sclerosus: a PCR-based study and review of the literature. J Cutan Pathol 2010;37:571–7.
[42] Moreno C, Kutzner H, Palmedo G, Goerttler E, Carrasco L, Requena L. Interstitial granulomatous dermatitis with histiocytic pseudorosettes: a new histopathologic pattern in cutaneous borreliosis. Detection of Borrelia burgdorferi DNA sequences by a highly sensitive PCR-ELISA. J Am Acad Dermatol 2003;48:376–84.

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[43] Oschmann P, Dorndorf W, Hornig C, Schafer C, Wellensiek HJ, Pflughaupt KW. Stages and syndromes of neuroborreliosis. J Neurol 1998;245:262–72.
[44] Mygland A, Ljostad U, Fingerle V, Rupprecht T, Schmutzhard E, Steiner I. EFNS guidelines on the diagnosis and management of European Lyme neuroborreliosis. Eur J Neurol 2010;17:8–16 [e11–14].
[45] Ogrinc K, Lusa L, Lotric-Furlan S, Bogovic P, Stupica D, Cerar T, et al. Course and outcome of early European Lyme Neuroborreliosis (Bannwarth Syndrome): clinical and laboratory findings. Clin Infect Dis 2016;63:346–53.
[46] Cerar T, Ogrinc K, Cimperman J, Lotric-Furlan S, Strle F, Ruzic-Sabljic E. Validation of cultivation and PCR methods for diagnosis of Lyme neuroborreliosis. J Clin Microbiol 2008;46:3375–9.
[47] Ackermann R, Horstrup P, Schmidt R. Tick-borne meningopolyneuritis (Garin-Bujadoux, Bannwarth). Yale J Biol Med 1984;57:485–90.
[48] Hansen K, Lebech AM. The clinical and epidemiological profile of Lyme neuroborreliosis in Denmark 1985–1990. A prospective study of 187 patients with Borrelia burgdorferi specific intrathecal antibody production. Brain 1992;115(Pt 2):399–423.
[49] Schwenkenbecher P, Pul R, Wurster U, Conzen J, Pars K, Hartmann H, et al. Common and uncommon neurological manifestations of neuroborreliosis leading to hospitalization. BMC Infect Dis 2017;17:90.
[50] Hansen K, Crone C, Kristoferitsch W. Lyme neuroborreliosis. Handb Clin Neurol 2013;115:559–75.
[51] Blanc F. [Neurologic and psychiatric manifestations of Lyme disease]. Med Mal Infect 2007;37:435–45.
[52] Grillon A, Scherlinger M, Boyer PH, De Martino S, Perdriger A, Blasquez A, et al. Characteristics and clinical outcomes after treatment of a national cohort of PCR-positive Lyme arthritis. Semin Arthritis Rheum 2018.
[53] Lipsker D, Hansmann Y, Limbach F, Clerc C, Tranchant C, Grunenberger F, et al. Disease expression of Lyme borreliosis in northeastern France. Eur J Clin Microbiol Infect Dis 2001;20:225–30.
[54] Steere AC, Schoen RT, Taylor E. The clinical evolution of Lyme arthritis. Ann Intern Med 1987;107:725–31.
[55] Steere AC. Lyme disease. N Engl J Med 2001;345:115–25.
[56] Cadavid D, Bai Y, Hodzic E, Narayan K, Barthold SW, Pachner AR. Cardiac involvement in non-human primates infected with the Lyme disease spirochete Borrelia burgdorferi. Lab Invest 2004;84:1439–50.
[57] Rostoff P, Gajos G, Konduracka E, Gackowski A, Nessler J, Piwowarska W. Lyme carditis: epidemiology, pathophysiology, and clinical features in endemic areas. Int J Cardiol 2010;144:328–33.
[58] Bateman H, Sigal L. Update on Lyme Carditis. Curr Infect Dis Rep 2000;2:299–301.
[59] Kostic T, Momcilovic S, Perisic ZD, Apostolovic SR, Cvetkovic J, Jovanovic A, et al. Manifestations of Lyme carditis. Int J Cardiol 2017;232:24–32.
[60] Forrester JD, Mead P. Third-degree heart block associated with lyme carditis: review of published cases. Clin Infect Dis 2014;59:996–1000.
[61] van der Linde MR. Lyme carditis: clinical characteristics of 105 cases. Scand J Infect Dis Suppl 1991;77:81–4.
[62] Mahne J, Kranjc BS, Strle F, Ruzic-Sabljic E, Arnez M. Panuveitis caused by Borrelia burgdorferi sensu lato infection. Pediatr Infect Dis J 2015;34:102–4.
[63] Wallet F, Labalette P, Herwegh S, Loiez C, Margaron F, Courcol R. Molecular diagnosis of a bilateral panuveitis due to Borrelia burgdorferi sensu lato by cerebral spinal fluid analysis. Jpn J Infect Dis 2008;61:214–5.
[64] Dietrich T, Geissdorfer W, Schlotzer-Schrehardt U, Holbach L, Schoerner C, Seitz B. Borrelia-associated crystalline keratopathy with intracorneal detection of Borrelia garinii by electron microscopy and polymerase chain reaction. Cornea 2008;27:498–500.
[65] Croskerry P. From mindless to mindful practice–cognitive bias and clinical decision making. N Engl J Med 2013;368:2445–8.
[66] Haddad E, Chabane K, Jaureguiberry S, Monsel G, Pourcher V, Caumes E. Holistic approach in patients with presumed Lyme borreliosis leads to less than 10% of confirmation and more than 80% of antibiotics failure. Clin Infect Dis 2018.

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