16th CONSENSUS CONFERENCE ON ANTI-INFECTIVE THERAPY

Lyme borreliosis: diagnosis, treatment and prevention

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Organized by the Société de Pathologie Infectieuse de Langue Française (SPILF) with the participation of the following scientific societies:

CMIT (Collège des Universitaires de Maladies Infectieuses et Tropicales)

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Introduction

In France, Lyme borreliosis is a zoonosis transmitted by the bite of a tick of the *Ixodes* genus (*Ixodes ricinus*) and is due to several genomic species of *Borrelia burgdorferi sensu lato*, essentially *B. Garinii*, *B. afzeliii, B. burgdorferi sensu stricto.*

Several classifications have been proposed based on the clinical features and natural history of the infection. We have adopted a 3-stage classification in order to take into account the pathophysiology:

- primary stage (*early localised Lyme borreliosis*): localised skin infection with a primary-secondary stage of systemic diffusion of *Borrelia*;
- secondary stage (*early disseminated Lyme borreliosis*): focal tissue infection (single or multiple);
- tertiary stage (*late Lyme borreliosis*): local lesions (role of *Borrelia* and inflammatory phenomena and/or immune disorders).

Question 1
What clinical and epidemiological features are suggestive of Lyme borreliosis?

The diagnosis of Lyme borreliosis is suggested by a history of possible exposure to a tick bite associated with clinical features.

Anti-*Borrelia* specific immunity does not prevent reinfection.

- **Erythema migrans** (EM) corresponds to the **primary phase** of the disease. It appears several days to several weeks after the tick bite and consists of an erythematous annular macula, several centimetres in diameter with centrifugal growth, often presenting central clearing.

  The presence of erythema migrans confirms the diagnosis.

- The **secondary phase** is only observed in the absence of antibiotic therapy during the primary phase, or when the primary phase remains undiagnosed. The clinical features of the secondary phase are mainly neurological and rheumatological.

  Early neuroborreliosis consists of meningo-radiculitis (presenting as nerve root pain and/or one or several cranial nerve palsies) or more rarely isolated meningitis, meningomyelitis or meningo-encephalitis.

  Lumbar puncture is indicated regardless of the neurological features in order to detect lymphocytic meningitis, an essential element of the diagnosis. However, in a patient with isolated peripheral nerve facial palsy, positivity serology is a sufficient argument to prescribe specific antibiotic therapy (grade C).

  Lyme arthritis, usually isolated, consists of monarthritis or oligoarthritis, almost always involving the knee.

Borrelial lymphocytoma, usually affecting the earlobe, nipple or external genitalia and diagnosed on the basis of clinical and pathological criteria (skin biopsy), cardiac lesions (benign conduction disorders) or ocular lesions are observed more rarely.

- The **tertiary phase** comprises neurological lesions (late neuroborreliosis) such as chronic encephalopathy and sensory polyneuropathy, usually associated with cerebrospinal fluid (CSF) abnormalities. Other neurological features can only be attributed to *Borrelia* infection in consultation with a specialist and in the presence of intrathecal synthesis of specific antibodies in the CSF (grade C).

  Acrodermatitis chronica atrophicans (asymmetrical inflammatory skin lesions on convex surfaces of the limbs with an atrophic course) and acute, recurrent or chronic arthritis may also be observed.

- The **post-Lyme syndrome** corresponds to a combination of chronic fatigue, diffuse pain and cognitive disorders following appropriately treated Lyme borreliosis, but the responsibility of active *Borrelia burgdorferi* infection has not been demonstrated. Resumption of antibiotic therapy does not modify the course of these symptoms (grade B).

Question 2
What is the place of laboratory tests in the diagnosis of the various forms of Lyme borreliosis?

The laboratory diagnosis of Lyme borreliosis is based on detection of antibodies directed against *Borrelia* antigens in the blood or CSF by the following techniques:

- immuno-enzymatic screening techniques (ELISA);
- immunoblotting confirmation techniques (Western blot).

Direct techniques (culture and PCR gene amplification) can contribute to the diagnosis in some atypical forms or can be proposed during epidemiological studies, but are not recommended in routine practice and are only available in a few specialized laboratories.
A minimum specificity of 90% of screening techniques is recommended.
An aid to interpretation of the results should be provided with an indication of the specificity of the reagent and its sensitivity for the main clinical forms of Lyme borreliosis.

The first-line diagnostic assessment must always comprise an ELISA test. When ELISA is negative, a confirmation test does not need to be performed. A positive or doubtful ELISA test must be confirmed by immunoblotting (Western blot).

An intense inflammatory syndrome is not usually observed in the course of Lyme borreliosis and should raise the suspicion of another diagnosis.

Recommendations for the laboratory diagnosis as a function of the clinical forms (grade C)		
Clinical forms	**Indications and results of the examinations essential for the diagnosis**	**Optional examinations****
Erythema migrans	NO examination	NONE
Early neuroborreliosis	- Lymphocytic reaction in CSF and/or raised CSF protein - Positive CSF serology, sometimes delayed in the blood - Intrathecal synthesis of specific IgG *	- Culture and PCR of CSF - Seroconversion or increase of serum IgG
Borrelial lymphocytoma	- Histological features of lymphocytoma - Positive serology (blood)	Culture and PCR of skin sample
Cardiac lesion	- Positive serology (blood)	According to specialist opinion
Arthritis	- Positive serology in blood usually with high titre (IgG) - Inflammatory synovial fluid	Culture and PCR of synovial fluid and/or tissue
Chronic neuroborreliosis	- Intrathecal synthesis of IgG specific*	Culture and PCR of CSF
Acrodermatitis chronica atrophicans	- Suggestive histological appearance - Positive serology with high titre (IgG)	Culture and PCR of skin sample***
Ocular forms	- Positive serology - Confirmation by specialist opinion	According to specialist opinion

* Intrathecal synthesis of IgG is determined by concomitant analysis of a blood sample and a CSF sample.

** These examinations are performed as second-line tests in particular situations: suggestive epidemiological and clinical context and negative first-line examinations.

*** Positive serology is necessary for the diagnosis of acrodermatitis chronica atrophicans; culture or PCR of a skin sample are only useful for epidemiological studies.

Situations in which serology is not indicated (grade C)
- Asymptomatic subjects - Systematic screening of exposed subjects - Tick bite with no clinical features - Typical erythema migrans - Systematic serology in treated patients

Question 3
What treatments can be recommended for Lyme borreliosis? What follow-up is necessary?

The objective of antibiotic therapy of Lyme borreliosis is complete eradication of *Borrelia* to prevent progression to secondary and tertiary forms. The objective of treatment is not to ensure negative serology.

The active molecules used in clinical practice belong to 3 classes: beta-lactams (penicillin G, amoxicillin, cefuroxime-axetil, ceftriaxone), tetracyclines (doxycycline) and macrolides (erythromycin, azithromycin). The various species of *B. burgdorferi sl*. present similar susceptibilities to these antibiotics. The skin and joint diffusion of beta-lactams, tetracyclines and macrolides is satisfactory. Central nervous system (CSF) diffusion is good for third generation parenteral cephalosporins, moderate for amoxicillin and poor for tetracyclines and macrolides. Macrolides and tetracyclines present an excellent intracellular diffusion.

Treatment guidelines are often based on old studies and were elaborated in order to ensure standardization and simplification of treatments, especially concerning the duration of treatment, in order to facilitate compliance.

- **Treatment of the primary phase (erythema migrans) (grade B)**
  - Amoxicillin and doxycycline have a comparable efficacy; oral treatment must be initiated as soon as possible after diagnosis of erythema migrans.
  - Doxycycline is contraindicated in children under the age of 8 years and in pregnant women or nursing mothers.

- The duration of treatment with amoxicillin and doxycycline is 14 days and should be prolonged to 21 days in the presence of multiple erythema migrans or erythema migrans accompanied by extracutaneous signs.
- Post-treatment **follow-up** is clinical. Skin signs may take more than a month to resolve without indicating treatment failure.

Guidelines for the management of the primary phase of Lyme borreliosis: oral treatment			
	ANTIBIOTIC	**DOSAGE**	**DURATION**
ADULTS			
First line	Amoxicillin or Doxycycline*	1 g t.i.d. 100 mg b.i.d.	14-21 days 14-21 days
Second line	Cefuroxime-axetil	500 mg b.i.d.	14-21 days
Third line when 1st and 2nd lines are contraindicated or in the case of allergy	Azithromycin**	500 mg once daily	10 days
CHILDREN			
First line < 8 years	Amoxicillin	50 mg/kg/day in three divided doses	14-21 days
> 8 years	Amoxicillin or Doxycycline*	50 mg/kg/day in three divided doses 4 mg/kg/day in two divided doses, maximum 100 mg/dose	14-21 days
Second line	Cefuroxime-axetil	30 mg/kg/day in two divided doses, maximum 500 mg/dose	14-21 days
Third line when 1st and 2nd lines are contraindicated or in the case of allergy	Azithromycin**	20 mg/kg/day as a single dose, maximum 500 mg/dose	10 days
PREGNANT WOMEN OR NURSING MOTHERS			
First line	Amoxicillin	1 g t.i.d.	14-21 days
Second line	Cefuroxime-axetil	500 mg b.i.d.	14-21 days
Third-line when 1st and 2nd lines are contraindicated or in the case of allergy Beyond the 2nd trimester of pregnancy	Azithromycin**	500 mg once daily	10 days

* A single dose of 200 mg/day can also be used (European Union of Concerted Action on Lyme Borreliosis - EUCALB) but has not been validated by a clinical trial.

** No justification for a loading dose (1 g) on D1 (EUCALB) in clinical trials.

➢ Treatment of secondary and tertiary phases (grade C)

Treatment guidelines for articular and neurological forms in adult are presented in the following table. For neurological forms, oral treatment is recommended only in the case of isolated facial palsy (FP), without associated meningitis, while parenteral therapy is recommended in all other cases.

Clinical situations	**Treatment options**	
	First line	**Second line**
Isolated facial palsy (FP)	Oral Doxycycline 200 mg/day for 14 to 21 days or oral Amoxicillin 1 g t.i.d. for 14 to 21 days or Ceftriaxone IV* 2 g/day 14 to 21 days	
Other forms of neuroborreliosis including FP with meningitis	IV* Ceftriaxone 2 g/day for 21 to 28 days	IV Penicillin G 18-24 MIU/day for 21 to 28 days or oral Doxycycline 200 mg/day for 21 to 28 days
Acute arthritis	Oral Doxycycline 200 mg/day for 21 to 28 days	Oral Amoxicillin 1 g t.i.d. 21 to 28 days
Recurrent or chronic arthritis	Oral Doxycycline 200 mg/day for 30 to 90 days or IM/IV Ceftriaxone 2 g/day 14 to 21 days	

* the IM route can also be used
MIU: Million International Units

- The first-line treatment of borrelial lymphocytoma is oral doxycycline (200 mg/day for 14 to 21 days).
- The recommended antibiotic for the treatment of cardiac lesions is IV ceftriaxone (2 g/day for 21 to 28 days).

- The treatment for acrodermatitis chronica atrophicans is oral doxycycline (200 mg/day for 28 days) or, alternatively, IV or IM ceftriaxone (2 g/day for 14 days).
- The treatment in children is identical to that in adults after taking age-related contraindications into account (tetracyclines are contraindicated before the age of 8 years) and dose adjustments as a function of weight and the site of infection (IV or IM ceftriaxone 75 to 100 mg/kg/day without exceeding 2 g/day).
- **Follow-up** is clinical and must be continued for several weeks to assess the efficacy of treatment with sufficient follow-up. The lesions resolve more slowly when treatment is delayed. Follow-up serology is not recommended, as the results are difficult to interpret. Longer or repeat courses of antibiotic therapy can be proposed in certain late forms of neuroborreliosis or arthritis.

Question 4
What preventive measures should be proposed?

A tick bite carries a risk of transmission of bacterial, viral and parasitic pathogens, which can justify specific preventive measures. Tetanus immunization must be systematically checked.

This consensus conference only assessed the measures designed to prevent transmission of Lyme borreliosis.

- **Primary prevention** is designed to avoid contact with ticks, the vectors of Lyme borreliosis:
  - Information of the general public, exposed subjects and health care professionals is therefore necessary (grade C) and must concern the following points:
    - the risk and modalities of transmission of *Borrelia burgdorferi sl.*, the pathogen responsible for Lyme borreliosis;
    - the various phases of the life cycle of ticks (see photograph) and the modalities of removal when they are attached to the skin;
    - the main clinical features of Lyme borreliosis, particularly the presenting signs;
    - the various prevention and treatment options.

Photograph: *Ixodes ricinus* (male and female adults, nymph, larva)

Collection Philippe Parola

- Barrier protection is recommended in endemic zones, consisting of long, closed protective clothing (grade C).

  Skin insect repellents are recommended in endemic zones, except in infants under the age of 30 months. Only IR 35/35 can be used in pregnant women. The efficacy of insect repellents is limited and they can be toxic. The mosquito repellents recommended by the French Health Products Safety Agency (AFSSAPS) are DEET, IR 35/35 and citriodiol and these recommendations can also be applied to ticks (grade C).

  Insect repellents for clothes (permethrin) can be used, except in young children, in highly endemic zones and in the case of repeated exposure, although only limited efficacy data are available for these products in relation to ticks (grade C).

- **Secondary prevention** is essentially based on the detection and rapid removal of ticks after exposure
  - ticks must be identified by meticulous examination of all of the skin, especially in the usual sites of tick bites (axillae, popliteal fossae, genital region, scalp) (grade C),
  - when a tick is attached to the skin, it must be removed as rapidly as possible by a mechanical method (fine forceps, tick tweezers). The risk of transmission of *Borrelia burgdorferi sl*., depends on the tick infestation rate and the duration of attachment of the tick to the skin. In France, there is a risk of transmission by the first hours of attachment; this risk increases with time and is high after 48 hours (grade B).
  - chemical substances (alcohol, ether, vaseline, petrol) should not be used to remove ticks due to the risk of regurgitation of the tick and transmission of *Borrelia burgdorferi sl.* (grade C).
  - after removing the tick, the bite must be disinfected. This zone must then be watched to detect the appearance of erythema migrans.

Systematic prophylactic antibiotics after a tick bite are not recommended.

In endemic zones, prophylactic antibiotics may be indicated in individual cases in situations with a high risk of contamination (multiple bites, long period of attachment, known high infestation rate): oral doxycycline as a single dose (200 mg) (grade A) or oral amoxicillin (3 g/day for 10 to 14 days) (grade B). Three particular situations should be distinguished in this context:

- in pregnant women: a risk of foetal infection or malformation has not been formally demonstrated and no specific guidelines are therefore proposed. When prophylactic antibiotics are prescribed, it is preferable to use oral amoxicillin (3 g/day for 10 days) (grade C);
- in children under the age of 8 years: there are no specific guidelines. When prophylactic antibiotics are prescribed, it is preferable to use oral amoxicillin (50 mg/kg/day for 10 days) (grade C);
- in immunodepressed subjects: there is a theoretical increased risk of dissemination of *Borrelia burgdorferi sl*. When prophylactic antibiotics are prescribed, it is preferable to use a single dose of oral doxycycline (200 mg) or oral amoxicillin (3 g/day) for 10 to 21 days depending on the severity of immunodeficiency (grade C).