Lyme Borreliosis

FROM PATIENT DIAGNOSIS TO DISEASE MANAGEMENT

The information in this booklet is given as a guideline only and is not intended to be exhaustive. It in no way binds bioMérieux, Inc. to the diagnosis established or the treatment prescribed by the physician.

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Lyme borreliosis became known worldwide after Lyme arthritis and then Lyme disease was reported in the United States in the 1970s, although the first descriptions of cutaneous manifestations of the disease had originated in Europe in the early 1900s.

This booklet addresses the main aspects of the epidemiology and biology of the disease, as well as the clinical management of this spirochetal infection. The last two sections cover several frequently asked questions as well as case studies.

We sincerely hope that this booklet will be of interest and help to all those involved in the care of patients with *Borrelia* infections.

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LYME BORRELIOSIS

1. HISTORY

The name comes from the town of Lyme in Connecticut (USA), where a number of unusual cases of arthritis were identified in the early 1970s. The mothers of a group of children who lived near each other in Lyme, Old Lyme and East Haddam made researchers aware that, among their children, many were diagnosed with juvenile rheumatoid arthritis.

On investigation, this arthritic disease was indeed shown to be unusually and highly prevalent among children in the counties of Old Lyme and Lyme: 1/10, whereas it was 1/1,000 in the normal population in other regions of the United States.

A retrospective study started in 1975 by A. Steere, S. Malawista and colleagues from Yale University led to the description of Lyme arthritis and then Lyme disease in 1977.

Unknown to many Americans, several non-articular manifestations of the disease had been previously described in Europe in the early 20th century: acrodermatitis chronica atrophicans (Herxheimer and Hartmann, 1902), erythema chronicum migrans (Lipschütz, 1913) and meningo-radiculitis (Garin and Bujadoux, 1922).

In 1949, S. Hellerström reported the first cases of erythema chronicum migrans (ECM) associated with meningitis successfully treated with penicillin.

In 1982 to 1984, a new Borrelia species was identified and then cultured by W. Burgdorfer, A. Barbour and colleagues as a pathogenic agent of the disease, which is transmitted through an infected tick bite.

2. EPIDEMIOLOGY

Most common and rapidly spreading vector-borne disease in the world.

Annual number of cases worldwide - estimated to be 85,500 - 118,500 (2009 figures):
- Europe: 65,500 – 85,000
- North America: 16,500 - 30,000
- Asia: 3,500
- North Africa: 10

However, significant under-reporting of Lyme borreliosis (LB) is likely, since it is not a mandatorily notifiable disease in some European and North American countries. Over-reporting is also likely since case definition criteria varies among countries.

In Europe, the highest incidence is reported in Austria, the Czech Republic, Germany, Slovenia.

In North America, the highest incidence is reported in the states of Connecticut and Rhode Island.

Impact of climate change: since the 90s, tick vectors have spread into higher latitudes and altitudes in Europe. Future climate change could facilitate this spread, leading to increased disease occurrence in endemic areas. In other areas, where conditions will become too hot and dry for tick survival, LB may tend to disappear.
3. CAUSATIVE AGENT: 
BORRELIA BURGDORFERI

Nearly 30 years have passed since the bacteria *Borrelia burgdorferi* was first described as the etiologic agent of Lyme disease. The *Borrelia* genus belongs to the order of spirochaetales, that also includes the genera *Leptospira* and *Treponema*, as human pathogens. These bacteria are vigorously motile and spiral-shaped.

The *Borrelia burgdorferi* sensu lato (sl) group currently includes 18 species, but Lyme borreliosis is mainly caused by three pathogenic species:

- **B. burgdorferi** sensu stricto (ss): found in the United States and Europe
- **B. afzelii**: found in Asia and Europe
- **B. garinii**: found in Asia and Europe

The *B. burgdorferi* lipoproteins allow the spirochetes to attach to mammalian cells and presumably help the spirochetes to adapt and survive in markedly different arthropod and mammalian environments. *B. burgdorferi* evades the host immune system through different mechanisms, including:

- CRASPs (Complement Regulatory Acquired System Protein), which inhibits complement cascade reaction,
- VlsE recombination, which is a complex antigenic variation system.
- OspA and OspB are expressed during the arthropod life of the spirochete and during the late phase of mammalian infection,
- BBK32 is a fibronectin protein expressed during the early phase of infection.

Some of these lipoproteins are well characterized:

- **OspC** (Outer surface protein C) is essential to establish *Borrelia* infection, essentially produced *in vivo*,
- **DbpA** (Decorin-binding protein A) outer surface protein produced by *Borrelia*, essentially *in vivo*,
- **VlsE** (Variable major protein-like sequence), expressed *in vivo* presents a highly immunogenic conserved region, used for serodiagnosis,
- **OspA and OspB** are expressed during the arthropod life of the spirochete and during the late phase of mammalian infection,
- **BBK32** is a fibronectin protein expressed during the early phase of infection.

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**Figure 2: Classification of Borrelia burgdorferi** (Adapted from M.V. ASSOUS, Cahiers de formation, Bioforma, 2005).

**Figure 3: B. burgdorferi spirochete**

- **Flagella**
- **Outer membrane**
- **Protoplasmic cylinder**

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- VlsE recombination, which is a complex antigenic variation system.

**KEY POINTS**

- Outer surface proteins (OspC, DbpA, VlsE...) play a major role in the immune response of the infected host.
- The VIDAS Lyme IgG assay contains a combination of 3 recombinant chimeric *Borrelia burgdorferi* sensu lato proteins (VlsE, DbpA, and OspC). The design of the chimeric protein constructs, which includes the VlsE invariant region IR6 (commonly known as C6), allow the VIDAS Lyme IgG assay to provide high sensitivity and specificity and help to reduce cross reactivity and the potential for interaction with other spirochetes.
4. VECTOR OF LYME DISEASE

BIOLOGY OF IXODES TICKS

Lyme borreliosis is a zoonosis transmitted by a hard tick, *Ixodes sp.* Ticks belong to the group of Acari, family of Ixodidae. The life cycle includes three life stages: the larva, the nymph and the adults.

Hard ticks are obligate blood-feeders, requiring one blood meal per life stage to molt. They stay attached to the vertebrate host for several days to complete the blood meal. The adult female feeds once, lays thousands of eggs and dies; the male does not take blood meal. *Ixodes* ticks feed on a wide variety of vertebrate hosts such as rodents, birds and cervids.

Hard ticks are very sensitive to desiccation, explaining that they are not found in dry areas. Ticks do not fly or jump and their bites are painless. They do not bite during winter time where they observe diapausis: their main activity is from March to end of November but varies from year to year according to the weather. The life cycle may be completed in 3 years, 2 years or even 1 year. Ticks quest on vegetation and await a host to perform their blood meal. Unfed ticks have a reddish body and a dark brown dorsal scutum.

IXODES AND THE TRANSMISSION OF BORRELIA

The mode of transmission is particularly efficient. Ticks secrete a variety of pharmacologically and immunologically active compounds that help the feeding process and increase the pathogenicity of the spirochetes. Depending on the geographic areas, up to 30 to 40% of nymphs can be infected by *B. burgdorferi* sl.

- Mammals such as small rodents, rats, squirrels, shrews..., birds such as passerines and pheasants, and deer constitute the wild reservoir. *B. afzelii* is more often associated with rodents and *B. garinii* more frequently with birds.
- In Europe, the main vector of *B. burgdorferi* sl is *Ixodes ricinus*.
- In the United States, the vector is *I. scapularis* on the East coast and *I. pacificus* on the West coast, both of which transmit *B. burgdorferi* ss.
- In Asia, the vector is *I. persulcatus*. 
Ixodes ticks acquire *B. burgdorferi* sl at any stage of the life cycle during an infective blood meal on a reservoir host. A complex migration and maturation process of the bacteria from the gut to the salivary glands explains that the disease is not readily inoculated and a delay of several hours is necessary for transmission. However, the pattern of transmission can vary from a few hours in Europe with *I. ricinus* to 2 to 3 days in the United States with *I. scapularis* infected with *B. burgdorferi* ss.

**KEY POINTS**

- Painless bite which may go unnoticed if no erythema.
- Erythema may appear and remain for several weeks.
CLINICAL DIAGNOSIS

Lyme borreliosis is a **multi-systemic disease** caused by bacteria from the *Borrelia burgdorferi* sensu lato group. The disease is usually divided into **three stages for didactic purposes**: early localised, early disseminated and late Lyme borreliosis.

1. EARLY LOCALISED LYME BORRELIOSIS

The first clinical sign of infection is the most frequent manifestation of Lyme borreliosis. It consists of a **cutaneous lesion called erythema migrans (EM)**.

![Erythema migrans](Photo credit: James Gathany, Public Health Image Library (PHIL), CDC)

A few days after the tick bite, this lesion typically begins as a red macula around the site of the bite, and slowly enlarges, reaching several centimeters in diameter over a period of days to weeks. EM skin lesions are typically round or oval but can also have an irregular shape. Central clearing of the lesion may appear, leading to its characteristic ring-like appearance. Untreated lesions may persist and expand over days to several months, leading to a lesion reaching > 50 centimeters in diameter.

2. EARLY DISSEMINATED LYME BORRELIOSIS

Early disseminated Lyme borreliosis occurs after the first stage of the disease only if the localised infection is left untreated or goes unnoticed. Clinical manifestations at this stage are mainly **neurological and articular**.

Borreliae may spread to the central and/or peripheral nervous system, causing various early neurological syndromes. Known as **early neuroborreliosis**, these syndromes include mainly lymphocytic meningitis and radiculoneuritis (resulting in peripheral facial palsy in case of facial nerve involvement).

**Joint manifestations** are more frequent in the United States than in Europe. They are characterized by inflammatory mono- or oligo-arthritis often preceded by intermittent migratory athralgias, typically involving large joints and most often the knee.

Other manifestations are more rarely observed at this stage:
- **ocular** (conjunctivitis, keratitis, scleritis, myositis, occlusion of the central vein of the retina),
- **borreial lymphocytoma** (frequently located on the ear lobe or in the region of areola mammae or scrotum),
- **cardiac manifestations** (mostly conduction disturbances).

3. LATE DISSEMINATED LYME BORRELIOSIS

The late stage of Lyme borreliosis comprises neurological, cutaneous and/or articular manifestations:

- **Chronic neurological manifestations** are called late neuroborreliosis and include mainly chronic encephalomyelitis and axonal sensitive polyneuropathy. Their etiological diagnosis is sometimes difficult.

- The **chronic skin manifestation** of the disease is *acrodermatitis chronic atrophicans* (ACA). ACA starts insidiously several months or years after the beginning of the infection with inflammatory lesions. The epidermidis is initially infiltrated and oedematous, then progressively becomes less inflammatory but more atrophic. The color of the skin lesions slowly becomes violaceous and thinner as the disease progress, causing underlying vessels to become visible under the skin.

- **Chronic rheumatologic manifestations** are mostly arthritis. These forms of arthritis differ from those of the early dissemination stage by their persistent features.

### Acrodermatitis chronica atrophicans


Lyme borreliosis should be considered only when clinical symptoms well described as compatible with the disease and/or objective physical findings of the disease are combined with a history of possible exposure to tick bites in known tick-infested areas.

The presence of a typical EM is the only pathognomonic sign enabling reliable clinical diagnosis of Lyme borreliosis, but ACA, ear lobe lymphocytoma and meningoradiculoneuritis are also highly supportive of the diagnosis.

Very few patients with Lyme borreliosis will present the full range of manifestations of the disease (EM after a tick bite followed by heart, articular or nervous system involvement and late involvement of joints, skin and nervous system). Moreover, the traditional division of Lyme disease evolution into stages is of great value for didactic purposes, but the appearance of clinical symptoms is usually less well defined.

Finally, many of the symptoms can also occur with other diseases. Therefore, **laboratory documentation of Lyme borreliosis is required** for all clinical manifestations of the disease, except for early skin lesions.

### Key Points

- Diagnosis is largely based on clinical symptoms (erythema migrans is pathognomonic) and the possibility of exposure to infected ticks.

- If clinical signs are non-specific or go unnoticed, the disease may be left untreated, and may evolve to severe and disabling manifestations.

- Biological tests are helpful when symptoms are not specific enough. Differential diagnosis is key to avoid risk of misdiagnosis.

- **EARLY, ACCURATE DIAGNOSIS IS KEY FOR SUCCESSFUL TREATMENT.**
LABORATORY DIAGNOSIS

Lyme borreliosis should be diagnosed primarily on the clinical presentation and a history of tick-exposure risk. Laboratory tests are helpful when LB is suspected in the presence of non-specific clinical manifestations.

1. METHODS FOR DIRECT DIAGNOSIS

■ CULTURE

Direct detection of *B. burgdorferi* sensu lato (*B. burgdorferi* s.l.) using culture techniques has a low sensitivity (except in EM skin lesion - up to 70%), usually ranging from 1% in Lyme arthritis to 15% in other manifestations, due to a weak viable spirochete burden in tissues. This technique is also time-consuming, invasive and requires the use of a specific medium and equipment. Therefore, **culture is not used in routine, but only occasionally to confirm atypical cases**, and in this case should be performed in reference laboratories.

■ MOLECULAR TESTING

DNA amplification by polymerase chain reaction (PCR) techniques are more often used by clinical laboratories since some commercial real-time PCR kits are now available. PCR assays are specific, generally targeting flagellin or outer surface protein genes (Osp). However, they are not yet standardized, resulting in variable sensitivity levels. Even though they allow the detection of a low number of *B. burgdorferi* s.l. in samples from untreated patients, these techniques still lack sensitivity. Higher sensitivity for synovial samples may be obtained by using tissue biopsies rather than fluids.


<table>
<thead>
<tr>
<th>SAMPLE TYPE</th>
<th>SENSITIVITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>EM skin biopsies</td>
<td>≅ 50-70%</td>
</tr>
<tr>
<td>Synovial biopsy and/or fluid of Lyme arthritis</td>
<td>≅ 50-85%</td>
</tr>
<tr>
<td>CSF of acute neuroborreliosis</td>
<td>≅ 15-30%</td>
</tr>
</tbody>
</table>

Therefore, **molecular assays are not relevant for first-line testing, but are helpful to investigate atypical manifestations**, especially when atypical cutaneous lesions, borrelial lymphocytoma or acrodermatitis chronica atrophicans (ACA) are suspected, or in cases of persistent arthritis.

2. METHODS FOR INDIRECT DIAGNOSIS

In routine, serodiagnostic techniques are used to screen and confirm a *Borrelia* infection via the detection of specific antibodies in patients. EUCALB (European Concerted Action on Lyme Borreliosis) and the CDC (Centers for Disease Control) recommend a two-step strategy:

- IgM/IgG screening using enzyme immunoassay (EIA) techniques,
- If result is positive or equivocal, Western-blot (immunoblot) assay to confirm the specificity of the antibodies detected.

These assays can be performed on plasma, sera or cerebro-spinal fluid (CSF). A rich pattern of antibodies, usually against several proteins of *B. burgdorferi* s.l. (fig. 5), indicates the high specificity of the humoral response generated by the pathogen.

![Figure 5: IgG Western-blot showing the diagnostic bands for confirmation of the specificity of humoral response in LB. Interpretation rules vary when using different whole cell lysate blots or different recombinant blots.](Wilske V, et al. MiQ 12 Lyme Borreliosis. Urban & Fischer Verlag. Munich. 2000. p. 1-59)
3. CHOICE OF LABORATORY TECHNIQUES ACCORDING TO THE STAGE OF BORRELIOSIS

Bacterial dissemination enhances a specific humoral response \textit{in vivo}. The stage of infection determines the choice of diagnostic techniques. When a patient consults for a tick bite, no serological investigation is required, but only a weekly clinical survey for at least one month.

The first visible manifestation of spirochete dissemination is \textit{erythema migrans} (EM). At this stage, only antibiotic therapy is required, and should be prescribed without delay. Serology is not helpful for diagnosis as this manifestation is pathognomonic. Moreover, after the infecting tick bite, the rise in IgM antibodies can only be detected after one or two months, then IgG seroconversion is observed one month later, in the absence of antibiotic therapy.

Further spirochete dissemination may lead to a transient spirochetemia. This marks the beginning of the secondary stage. Symptoms are no longer specific, and serological investigations are relevant to establish an accurate diagnosis. Serum for detection of specific antibodies is easy to collect, but when a neuroborreliosis (NB) is suspected, both serum and CSF should be analyzed to detect an intrathecal production of specific antibodies against \textit{B. burgdorferi} sl.

- The \textbf{cerebro-spinal fluid (CSF) titer index} can be determined as the ratio of (ELISA titer in CSF/ELISA titer in serum) to (albumin in CSF/Albumin in serum).

\[
\text{Intrathecal Antibody Production (IAP)} = \frac{\text{TIBBLING METHOD}}{\text{REIBER METHOD}}
\]

\[
= \frac{\text{(Lyme IgG CSF index / Lyme IgG serum index)}}{\text{(CSF albumin titer / serum albumin titer)}}
\]

An alternative IAP determination method can also be used:

\[
= \frac{\text{CSF total IgG titer / serum total IgG titer)}}{\text{(Lyme IgG CSF index / Lyme IgG serum index)}}
\]

The same method should be used to titer Lyme IgG / total IgG in both the blood and the CSF sampled at the same time.

Serological techniques show acceptable standardization, sensitivity and specificity - but they have limitations.

- In the early phase of borreliosis, the absence of antibodies does not mean absence of infection. Neither does the presence of antibodies indicate an active infection, as antibodies can persist several months or years after successful antibiotic therapy.

- The positive and negative predictive values of serology depend on the sensitivity and the specificity of the assays, but also on the prevalence of the disease in the population. Serological results should be interpreted with caution, especially in non-endemic areas.

In the late stage of the disease, the IgG antibody level is usually high, regardless of the clinical symptoms (NB, arthritis, ACA).

Diagnosis is finally confirmed by anamnesis, clinical symptoms and a positive serology.

Figure 6: Detection of immunological response following a bite from a tick infected with \textit{Borrelia burgdorferi}.

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**Table 3: Clinical manifestations of Lyme borreliosis and recommendations for the use of laboratory testing**

<table>
<thead>
<tr>
<th>CLINICAL MANIFESTATION</th>
<th>LABORATORY EVIDENCE: ESSENTIAL</th>
<th>LABORATORY/CLINICAL EVIDENCE: SUPPORTIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema migrans (a)</td>
<td>None</td>
<td>- Detection of (B. burgdorferi) s.l.(^*) by culture and/or PCR from skin biopsy</td>
</tr>
<tr>
<td>Neuroborreliosis</td>
<td>Pleiocytosis and detection of intrathecal specific antibody synthesis (b)</td>
<td>- Detection of (B. burgdorferi) s.l. by culture and/or PCR from CSF - Intrathecal synthesis of total antibodies - Specific serum antibodies - Recent or concomitant EM</td>
</tr>
<tr>
<td>Borrelial lymphocytoma (rare)</td>
<td>Seroconversion or positive serology (c), histology in unclear cases</td>
<td>- Histology - Detection of (B. burgdorferi) s.l. by culture and/or PCR from skin biopsy - Recent or concomitant EM. Detection of (B. burgdorferi) s.l. by culture and/or PCR from skin biopsy</td>
</tr>
<tr>
<td>Acrodermatitis chronica atrophicans</td>
<td>High level of specific IgG antibodies</td>
<td>- Histology</td>
</tr>
<tr>
<td>Lyme arthritis</td>
<td>High level of specific IgG antibodies</td>
<td>- Detection of (B. burgdorferi) s.l. by culture and/or PCR from synovial fluid</td>
</tr>
<tr>
<td>Lyme carditis</td>
<td>Specific serum antibodies</td>
<td>- Detection of (B. burgdorferi) s.l. by culture and/or PCR from endomyocardial biopsy</td>
</tr>
<tr>
<td>Ocular manifestation (rare)</td>
<td>Specific serum antibodies</td>
<td>- Recent or concomitant Lyme borreliosis symptoms - Detection of (B. burgdorferi) s.l. by culture and/or PCR from ocular fluid</td>
</tr>
</tbody>
</table>

\(^*\) \(B. burgdorferi\) s.l.: \(B. burgdorferi\) s.l.

(a) If lesion is <5 cm in diameter, a history of tick-bite and a delay before appearance of at least 2 days (after the tick bite) as well as an expanding rash at the site of the tick-bite is required.

(b) In early cases, intrathecally produced specific antibodies may still be absent.

(c) As a rule, initial and follow-up samples should be tested in parallel to avoid inter-assay variation.
Figure 7: Algorithm for diagnostic decision-making when LB is suspected

1. **Tick Exposure Risk and/or Tick Bite Memory**
   - Absence of clinical manifestations
   - No test/treatment required

2. **Clinical Surveillance for at least one month**
   - Compatible manifestation in skin, nervous system, joint, heart or eye (rarely)

3. **Serology Screening**
   - ELISA IgM and IgG on serum/plasma samples
   - Negative
   - Positive or equivocal

4. **Confirmation by Western Blot**
   - IgG or IgM on serum/plasma
   - Positive
   - Negative or equivocal

5. **PCR on Biological Fluids/Biopsy Tissue**
   - Negative
   - Positive

6. **Other Diagnosis**
   - Antibiotic Therapy

7. **Lyme Borreliosis Diagnosis Confirmed**
   - Antibiotic Therapy
PREVENTION & TREATMENT

1. TICK BITE PREVENTION

■ AVOID TICK BITES

The best prevention for humans relies on the avoidance of tick bites since no vaccine is available to prevent the disease. The use of protective clothing and tick repellents are adequate measures to decrease the risk of tick bites. Light-colored clothing with long pants tucked into socks facilitate the detection of ticks.

■ USE A REPELLENT

Four main cutaneous repellents have demonstrated their efficiency against ticks.

- **DEET** (diethyl toluamide) is the most ancient and the most commonly used, especially in USA.
- **KBR 3023** (1-piperidine carboxylic acid, 2[2-hydroxyethyl]-, methylpropylester) is also known as picaridin (commercial name: BAYREPEL®).
- **IR3535** (3-[N-acetyl-N-butyl] aminopropionic acid ethyl ester).
- **PMD** (para-menthane-3,8-diol or Citriodiol®) isolated initially from the lemon eucalyptus, *Corymbia citriodora* can also be used.

Essential oils are not effective enough to provide sufficient protection from ticks, since they are too volatile. These repellents must be used according to the manufacturers instructions.

People particularly exposed to tick bites can wear clothing impregnated with pyrethrin.

■ CHECK FOR TICK BITES

When returning from endemic areas, the most efficient prevention is to immediately and carefully check the body, including the scalp. In the event of a tick bite, use a tick remover. Various commercial devices are available. Grasp the tick as close to the skin surface as possible and turn it. Then disinfect the area and wash hands. The area of the tick bite should be observed for signs of Lyme borreliosis over a period of a few weeks.

■ HOW TO REMOVE A TICK

- Avoid folklore remedies such as “painting” the tick with nail polish or petroleum jelly, or using heat to make the tick detach from the skin. Your goal is to remove the tick as quickly as possible—do not wait for it to detach.
- Use fine-tipped tweezers to grasp the tick as close to the skin’s surface as possible.
- Pull upward with steady, even pressure. Don’t twist or jerk the tick; this can cause the mouth-parts to break off and remain in the skin. If this happens, remove the mouth-parts with tweezers. If you are unable to remove the mouth easily with clean tweezers, leave it alone and let the skin heal.
- After removing the tick, thoroughly clean the bite area and your hands with rubbing alcohol, an iodine scrub, or soap and water.
- Dispose of a live tick by submersing it in alcohol, placing it in a sealed bag/container, wrapping it tightly in tape, or flushing it down the toilet. Never crush a tick with your fingers.

■ FOLLOW UP

If you develop a rash or fever within several weeks of removing a tick, see your doctor. Be sure to tell the doctor about your recent tick bite, when the bite occurred, and where you most likely acquired the tick.
Figure 4: “Barriers” providing protection against infection.

KEY POINTS

- A tick bite does not necessarily mean infection.
- An infection does not necessarily mean illness.
- Several layers of “barriers” provide protection against Lyme disease.

Adult tick on a human host

Photo credit: Strle F, Stanek G.
3. TREATMENT

Patients showing compatible symptoms supported by adequate laboratory evidence for diagnosis should be treated to eradicate *Borrelia* and prevent possible progression of the disease (EUCALB, 2011).

### TREATMENT RECOMMENDATIONS

EUCALB, 2011; IDSA (Infectious Diseases Society of America), 2006

1 - Early Lyme borreliosis (see dosages in table 1)

- Early localized or disseminated Lyme borreliosis associated with *erythema migrans*: in the absence of specific neurologic or cardiac manifestations, oral treatment is preferred and should be started as early as possible.
  
  Doxycycline, amoxicillin or cefuroxime-axetil for 14 days is recommended. Macrolide antibiotics (azithromycin) could be an alternative for patients who cannot take beta-lactamines or doxycycline.

- Early neurologic Lyme borreliosis
  
  The use of ceftriaxone IV for 14 days is recommended. Doxycycline (EUCALB), Cefotaxime IV (IDSA) or Penicillin G may be an acceptable alternative (see dosages in table 1).

- Early cardiac manifestations of Lyme borreliosis
  
  Patients may be treated with either oral or parenteral antibiotic therapy for 18 days (IDSA) or 21 days (EUCALB). Doxycycline, amoxicillin or ceftriaxone is recommended as initial treatment.

2 - Late disseminated Lyme borreliosis (see dosages in table 1)

- Lyme arthritis
  
  Doxycycline, amoxicillin (or cefuroxime-axetil – IDSA) is recommended for 18 days (IDSA) or 21 days (EUCALB).

- Persistent or recurrent joint swelling
  
  Patients should be treated a second time with a 4-week course of oral antibiotics or a 2-4-week course of ceftriaxone IV.

- Neurologic disease
  
  Ceftriaxone IV for 2-4 weeks is recommended. Response to treatment is usually slow and may be incomplete.

### Table 1: General recommendations for antimicrobial regimens for the treatment of patients with Lyme borreliosis (adapted from EUCALB and IDSA guidelines).

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSAGE FOR ADULTS</th>
<th>DOSAGE FOR CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORAL REGIMENS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>500 mg 3 times per day</td>
<td>25-50 mg/kg per day in 3 divided doses (maximum 500 mg per dose)</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>100 mg twice per day¹</td>
<td>Not recommended in children &lt;8 years. For children aged &gt;8 years, 4 mg/kg per day in 2 divided doses (maximum 100 mg per dose)</td>
</tr>
<tr>
<td>Cefuroxime-axetil</td>
<td>500 mg twice per day</td>
<td>30-40 mg/kg per day in 2 divided doses (maximum 500 mg per dose)</td>
</tr>
<tr>
<td><strong>PARENTERAL REGIMEN</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>2 g intravenously once per day</td>
<td>50-100 mg/kg intravenously per day in a single dose (maximum 2 g)</td>
</tr>
</tbody>
</table>

¹. Tetracyclines are relatively contra-indicated in pregnant or lactating women and in children <8 years of age.

### Acrodermatitis chronica atrophicans (ACA)

ACA may be treated with doxycycline, amoxicillin and cefuroxime-axetil for 21 days.

### KEY POINTS

- If Lyme disease is diagnosed at an early stage, it can be successfully treated with antibiotics.
- Good antibiotic tolerance is observed, with few side effects.
- However, if left untreated, infection can spread to the joints, heart, and nervous system.
How to manage a patient presenting with a tick bite?

- If not already done, extract the tick as early as possible and disinfect the wound. Do not test the tick for presence of Borrelia DNA.
- Examine the patient for presence of erythema migrans (EM). If an erythema migrans is present, start antibiotic treatment.
- Monitor the tick bite area for one month.
- If no EM is present, but a suspicion of Lyme borreliosis remains (see Table 3, page 20), perform serological tests to confirm the diagnosis. Refer to algorithm in Figure 7 (page 22).

Why perform serological testing?

- Detection of spirochetes from biopsies (cutaneous, synovial) or biological fluids (blood, CSF or synovial fluid), by direct staining, culture or amplified molecular methods is difficult and therefore reserved for specialized laboratories and indicated for atypical lesions.
- Serological testing for antibodies directed to B. burgdorferi sl is the most common method for the biological documentation of early disseminated and late disseminated Lyme borreliosis manifestations.
- The 16th Consensus Conference on Anti-Infective Therapy – Lyme borreliosis: diagnosis, treatment and prevention, EUCALB and the CDC recommend use of a two-tier testing approach for the serological diagnosis of Lyme Borreliosis:
  1) Detection of specific antibodies should be performed first using an enzyme immunoassay (EIA) screening technique.
  2) Only positive or equivocal specimens should then be tested using an immunoblotting confirmation technique (Western blot). Because sensitivity and specificity of EIA and Western Blot vary in relation to the timing of specimen acquisition, clinical and exposure history must always be considered in the interpretation of serological results.

Why perform a lumbar puncture?

- Lumbar puncture enables detection of intrathecal antibodies in CSF and is essential to confirm a diagnosis of neuroborreliosis. According to IDSA guidelines (2006), less than 10% of untreated patients will evolve to develop neuroborreliosis.
- Analysis of CSF will typically show a lymphocytic pleocytosis and an intrathecal B. burgdorferi-specific antibodies synthesis.
- Analysis of the CSF must also be done in case of early neurological manifestations with seronegative results.

How to treat Lyme borreliosis in pregnant women?

- Pregnant patients with a reliable diagnosis of Lyme borreliosis should be treated by intravenous therapy.
- Breast-feeding patients may be treated in the same way as non-pregnant patients with the same clinical manifestations, except that doxycycline should be avoided (see table 1, page 15).

When should a patient be referred to a reference center?

- If there is a possibility of atypical manifestations (atypical EM, multiple EM, suspicion of ACA, atypical neurological manifestations…).
- In case of adverse reactions to antibiotic treatment.
- If need for expert interpretation of serological results.
- If culture of Borrelia from human specimens is required.
PATIENT A  ▶ EARLY NEUROBORRELIOSIS

A 55-year old male presents with pain in lower right leg and loss of feeling in L5 territory, one month after removing a tick from his abdomen.

How to confirm a diagnosis of neuroborreliosis?

▶ Perform Lyme borreliosis serology on serum/plasma and request lumbar puncture (LP) to perform serology on cerebro-spinal fluid (CSF) to detect intrathecal antibodies.
▶ In parallel, request CSF cytology and protein analysis.
▶ If CSF shows lymphocytic pleocytosis and specific intrathecal antibodies, diagnosis of early neuro-borreliosis is confirmed.
▶ Treat patient with ceftriaxone (2 g / day for 21 days) or alternative regimen.

What is your diagnosis?

▶ Although this lesion does not show the characteristic “ring-like” or “bull’s eye” appearance of EM, Lyme disease with EM should be the first hypothesis.
▶ Patient should be treated by oral antibiotic regimen to prevent *Borrelia* dissemination.
▶ There is no need for serological follow-up.

PATIENT B  ▶ ERYTHEMA MIGRANS (EM)

30-year old male presents with this non-pruriginous lesion. When questioned, he explains that the lesion has increased in size during the fortnight preceding the consultation. He consulted another doctor the prior week, who prescribed a Lyme serology test that was negative. The patient does not recall having any tick bite, but was in a wooded area 3 weeks previously.
BIBLIOGRAPHY

LYME BORRELIOSIS

- CDC. Reported cases of Lyme Disease by Year, United States, 1995-2009.

CLINICAL DIAGNOSIS

Differential diagnosis of Lyme borreliosis in just 27 minutes

- **SEROLOGICAL PROFILE**
- **HIGH SPECIFICITY AND SENSITIVITY**
- **EASY RESULT INTERPRETATION**
- **COST EFFECTIVE, STREAMLINED WORKFLOW**

### TECHNICAL SPECIFICATIONS

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<th>Abbreviation</th>
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<td>ACA</td>
<td>Acrodermatitis chronic atrophicans</td>
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<td>B.b.</td>
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<td>CRASPS</td>
<td>Complement regulatory acquired system protein</td>
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