Lyme Disease (Borreliosis) and Relapsing Fever — Diagnosis and Stages

In the following article, we present you all the relevant facts, tips and exam questions from the first symptoms to the treatment of the infection with borrelia.

Definition of Lyme Disease

Lyme disease is a disease that is caused by the infection with bacteria of the species Borrelia burgdorferi, borrelia mayonii, borrelia afzelli and borrelia garinii. These
belong to the family of gram-negative spirochetes. The agents are transmitted to humans via bites of infected black-legged ticks known as deer ticks. The ticks are more common in grassy and woody areas of the environment. The disease manifests itself in different organs; particularly affected are the skin, the neuro system and the joints.

**Synonyms:** Lyme-Borreliosis, Neuroborreliosis, Lyme disease.  
The Lyme-Borreliosis is named after the village Lyme (Connecticut, USA). It was in this village, where joint inflammations have occurred frequently. W. Burgdorfer discovered the agent in 1981, but the skin manifestations had already been described in Europe before.

**Epidemiology of Lyme Disease**

**Prevalence of Lyme-Borreliosis**

Lyme Borreliosis represents the most frequently transmitted disease via ticks in Europe.

- 5 - 35% of the ticks are infected with borrelia.
- The infection can occur from March to October, the critical period is from June to July.
- The regional spread of the infected ticks applies differently in various locations and should be considered for the diagnosis.
Etiology and Pathogenesis of Lyme Disease

Agents of Lyme-Borreliosis

The Borreliosis is caused by different species of borrelia, that all belong to the complex *Borrelia burdoferei sensu lato*. The following 4 human-pathogenic species are most often represented:

![Image: Using darkfield microscopy technique, this photomicrograph, magnified 400x, reveals the presence of spirochete, or “corkscrew-shaped” bacteria known as Borrelia burgdorferi, which is the pathogen responsible for causing Lyme disease. Borrelia burgdorferi are helical shaped bacteria, and are about 10 – 25µm long. These bacteria are transmitted to humans by the bite of an infected deer tick, and...]

Note: This map demonstrates an approximate distribution of predicted Lyme disease risk in the United States. The true relative risk in any given county compared with other counties might differ from that shown here and might change from year to year. Risk categories are defined in the accompanying text. Information on risk distribution within states and counties is best obtained from state and local public health authorities.
Borrelia burgdorferi sensu stricto

- Borrelia garinii
- Borrelia afzelii
- Borrelia spielmani

Reservoir of the Borrelia

- Small rodents and birds.
- Deer and roes are animal hosts for ticks.
- A couple of hundred vertebrate species are potential hosts for the vectors (hard ticks).

Path of infection and pathogenesis of the Lyme Borreliosis

In Central Europe, borrelia bacteria are transmitted via the bite of the hard tick *Ixodes (I.) ricinus und Ixodes scapularis*. The ticks can get from low vegetation (1,5 m) to humans.

**Note:** With the attachment period, the risk of disease increases significantly. The attachment period is becoming dangerous from 24 hours on. Certain surface proteins of the borrelia bacteria ensure that these can attach to the host cells. Also, pro-inflammatory cytokines are released.

**More different immune mechanisms are discussed:**

- Induction of autoantibodies against neuronal and glial antigens.
- Cross-reactivity of borrelia antibodies with neuronal antigens.
- T-cell-mediated immune response.

Borrelia bacteria can survive for many years in the host, for example, in phagocytes.
Risk groups are forestry workers, hunters, farmers and hikers.

Incubation period: 4 to 18 days

Symptoms and Clinic of Lyme Disease

Staging for Borreliosis

There are three stages to the symptomatology of a Borreliosis:

Stage I Week 1 - 5

Incubation period: Weeks to months

[Image: Erythema migrans - erythematous rash in Lyme]

Creation of the Erythema chronicum migrans, a bull’s eye rash that is appearing about 2 weeks after a tick bite. This skin reaction corresponds to the local spread of the agent in the dermis. Just half of the patients, that are experiencing stage II, have the Erythema migrans. Furthermore, symptoms, such as fever, myalgia, arthralgia and weariness can occur. Typically, the patients without the symptoms are having issues in the respiratory tract (flu without a cough, sputum or rhinitis).

Note: The Erythema chronicum migrans may not occur!

Stage II

Incubation period: Weeks to months

Meningoradiculitis: Radicular pains (Bannwarth-syndrome), partly radicular paresis, peripheral facial palsy (often at both sides). Also joint involvement, Myocarditis, pericarditis or Lymphadenosis cutis benigna. The latter describes a reactive hyperplasia of the lymphatic cells. The Lymphadenosis cutis benigna manifests itself mainly in terms of bluish-red nods in the skin, for example, near the earlobe.

Stage III
Incubation period: Months to years

The patients suffer from Acrodermatitis chronica atrophicans Herxheimer. This dermatologic manifestation of the Borreliosis has chronic-progressive stages, mostly affected are the extensor sides of the extremities. First, there is an edema. In addition, an atrophy of the subcutis is developing, so the subcutaneous fat; thereby, the thickness of the skin becomes reduced and the vessels beneath the skin can shine through. Finally, the affected parts of the skin will become sclerotic and develop a significant thickening that is hairless.

Other symptoms include Lyme arthritis with a 90% manifestation in the knee joint. The symptoms appearing in the stage III of a chronic Neuroborreliosis are:

- Encephalomyelitis: Paraparesis, Tetraparesis
- Neuritis n. optici
- Distal-symmetric Polyneuropathy
- Ataxia
- Bladder dysfunction
- Dyseaesthesias, asymmetric radicular signs of paralysis
- Heart problems such as irregular heartbeat.
- Hepatitis.
- Severe fatigue.

There is also a possibility of an eye involvement with uveitis, keratitis, episcleritis and retinal vasculitis.

**Note:** The staging for Borreliosis should be considered as a theoretical construct, as it is too artificial.

For the clinical classification, the categorization is considered in an early and late manifestation of the disease:

- **Early manifestation** (located: Erythema migrans; disseminated: e.g. acute Neuroborreliosis)
- **Late manifestation** (arthritis, acrodermatitis and chronical neuroborreliosis)

**Diagnostic and Therapy of Lyme Disease**

The Lyme-Borreliosis is primarily a presumptive clinical diagnosis. This will be supported by the medical history and laboratory diagnostics. 80 – 90% of the patients with clinical Neuroborreliosis will have the suspicion confirmed by a specific intrathecal antibody synthesis.

**Pathogen detection: Serology-Step-by-Step diagnosis**

1. **ELISA (or immunofluorescence test):** Verification of antibodies (IgM/ IgG) against B. burgdorferi in the enzyme linked immunoabsorbent assays tests.
   Warning: the increase of the borrelia-antibodies doesn’t have to be always detectable, or can also happen to be detectable a couple of days after the tick bite. The antibodies are not appropriate for the evaluation of the therapeutic process!
   After a successful antibiotherapy, the antibodies can also, over months to years, circulate in the cerebrospinal fluid. If the test for the first stage is positive, follow 2.

2. **Immunoblot (Western Blot):** As confirmation test.

A positive antibody finding and corresponding clinical findings suggest Lyme-Borreliosis.
**Note:** If there is at the same time an infection with syphilis, it may happen that false positives findings are found because of cross-reactions (TPHA test!).

**Overview of the Diagnostic and Therapy of the 3 Stages of Borrelia**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Diagnostic</th>
<th>Therapy</th>
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<tbody>
<tr>
<td><strong>Stage I</strong></td>
<td>Medical history of tick bites (50% of the patients don’t remember). Antibody detection in blood (successful in just 40%).</td>
<td><strong>Doxycyclin</strong> or <strong>Erythromycin</strong> p.o. for 2 weeks, for children and pregnant women: Amoxicillin and Cefuroxime, in case of intolerance: Azithromycin</td>
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<tr>
<td><strong>Stage II</strong></td>
<td>IgG-Antibody detection in blood, confirmation test with Western Blot. For Lyme-arthritis: agent detection in punctate.</td>
<td><strong>Cephalosporin of the 3. Generation</strong> (e.g. Ceftriaxone) Penicillin G intravenous for 2 – 3 weeks if symptoms are particularly severe.</td>
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<tr>
<td><strong>Stage III</strong></td>
<td>Antibody detection in blood and liquor examination: lymphocytic Pleocytosis, increased percentage of protein, intrathecal Borrelia-specific IgG/IgM-Antibodies, occasionally direct pathogen tests (Borrelia-DNA).</td>
<td><strong>Cephalosporin of the 3. Generation</strong> intravenous for 2 – 3 weeks.</td>
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**Differential diagnosis of Lyme Disease**

Dependent on the stage of the disease, there are many possibilities that can be considered for a differential diagnosis:

- Disease with an infection via ticks: FSME, Anaplasmosis, Rickettsiosis
- Neurological symptoms: multiple sclerosis
- Joint inflammations: activated arthrosis, rheumatoid arthritis
- If therapy is unsuccessful: search for tumors

**Prophylaxis and Prevention of Lyme Disease**

If the tick is removed within the first 12 hours, the risk to be infected with borrelia is very low. For the removal, a tick tweezer should be used. For persons from non-endemic areas, there is no need for prophylactic antibiotics, but the side of injection should be observed.

**Precautions against ticks:**

- Adequate clothing
- Repellents
- Scanning the body for ticks after being outside (focus on axillary and inguinal regions!)
- Create a tick-proof yard by clearing brush and leaves where ticks live and keeping woodpiles in sunny areas.
- Remove ticks from bite site as soon as possible and do not assume immunity is developed after an initial infection.

**Note:** There is no vaccine against Borreliosis yet. A person who already suffered from Borreliosis is not immune to a re-infection.
Complications of Lyme disease

- Chronic joint inflammation (Lyme arthritis)
- Neurological symptoms such as facial palsy and neuropathies.
- Impaired memory.
- Irregular heart rhythm

Epidemic and Endemic Relapsing Fever

**Facts to the relapsing fever in an overview.**

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<thead>
<tr>
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<th>Epidemic relapsing fever</th>
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<tbody>
<tr>
<td><strong>Agents</strong></td>
<td>Borrelia recurrentis.</td>
<td>Borrelia duttoni.</td>
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<tr>
<td><strong>Transmission</strong></td>
<td>Lice (Pediculus humanus), “Relapsing fever due to lice,” mainly in the cold season; lack of hygiene</td>
<td>Lederzecken (Ornithodorus), “Recurrent fever” in Germany just known as imported travel disease.</td>
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<td><strong>Pathogenesis</strong></td>
<td>Pyrogenic effects by cell wall antigens.</td>
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<td><strong>Symptoms</strong></td>
<td>Recurrent fever for 3 – 6 days, symptom-free intervals, chills, arthralgias, myalgias, stomach aches, hepatosplenomegaly, diffuse petechial hemorrhages, pinpoint large macular exanthema.</td>
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<tr>
<td><strong>Complications</strong></td>
<td>30% of the patients develop seizures, coma, hemiplegia, CNS-bleedings, myocarditis with arrhythmia, liver failure.</td>
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<tr>
<td><strong>Diagnostic</strong></td>
<td>Serological diagnostics is unreliable! Detection of the pathogens in peripheral blood via dark-field microscopy.</td>
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<tr>
<td><strong>Therapy</strong></td>
<td>Erythromycin, alternatively Tetracyclind</td>
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<tr>
<td><strong>Lethality</strong></td>
<td>2 – 5%</td>
<td>Up to 40%</td>
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Review Questions

The correct answers can be found below the references.

1. Which antibiotic should be prescribed for pregnant women, if a drug therapy for Borreliosis is indicated?
   - A. Doxycyclin
   - B. Amoxicillin
   - C. Ciprofloxacin
D. Vancomycin
E. Erythromycin

2. A 21-year-old teacher, who until now was never seriously sick, shows the following symptoms (in March): slight fever, flushing of the face and symptoms of a cold. She goes to the Doctor's surgery. The physical examination shows exanthemas in the extremities. Which diagnosis does fit the most?

A. Exanthema subitum
B. Lyme-Borreliosis
C. Erythema infectiosum
D. Rheumatic nodules
E. Measles

3. The initial manifestation of the borreliosis consists probably of an ...

A. ...Erythema anulare centrifugum
B. ...Erythema (exsudativum) multiforme
C. ...Erythema infectiosum
D. ...Erythema nodosum
E. ...Erythema (chronicum) migrans

References


Correct answers: 1B, 2C, 3E

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