Deutsche Borreliose-Gesellschaft e. V.

Diagnosis and Treatment of Lyme borreliosis

Guidelines

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Diagnosis and Treatment of Lyme borreliosis (Lyme disease)

Guidelines of the German Borreliosis Society

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Guidelines are presented as recommendations. They are intended to help physicians to arrive at decisions. They are neither legally binding on physicians nor do they form grounds for substantiating or indemnifying from liability.

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Content

List of tables

List of abbreviations

ELISA	Enzyme-Linked Immunosorbent Assay
EM	Erythema migrans
LB	Lyme borreliosis
LTT	Lymphocyte transformation test

1. Preliminary remarks

Lyme borreliosis was identified as a disease in its own right in 1975 by Steere et al.[139] and the causative agent was discovered in 1981 by Willi Burgdorfer.[21] In spite of intensive research, there is as yet an inadequate scientific basis for the diagnosis and treatment of Lyme borreliosis. This is especially the case with the chronic forms for which there is a lack of evidence-based studies.

The recommendations for antibiotic treatment presented in the Guideline differ significantly in some respects from the guidelines of other specialist societies. The patient must be made aware of this fact when he is treated according to this Guideline. In addition, careful checks for side-effects must be carried out when long-term antibiotic therapy is conducted.

Lyme borreliosis is listed in the ICD-10-GM Diagnosis Code under A 69.2 “Lyme disease, Erythema chronicum migrans due to B. burgdorferi” and under M 01.2 “Arthritis in Lyme Disease”.

2. Diagnosis of Lyme borreliosis

The earlier classification of the course of the disease into an initial stage (Stage I) with the principal symptom of erythema migrans, a second stage (Stage II) with early organ manifestations after dissemination of the pathogens, and a third stage of the disease (Stage III) with late manifestations of Lyme borreliosis, is outdated as the clinical signs of the various stages overlap. Today, classification into early and late manifestations of LB is preferred. In this classification, the early stage is equivalent to Stages I / II and the late stage is equivalent to Stage III. The term “chronic Lyme borreliosis” is equivalent to Stage III.

2.1 Essential features of Lyme borreliosis

Lyme borreliosis occurs throughout Europe. One can be infected mainly in the countryside, in one’s garden or through contact with domestic and wild animals.

As Lyme borreliosis can affect many organs (it is known as a multiorgan disease), a wide range of differential diagnoses arise for the often numerous manifestations of the disease.

Essential features of LB:

- Erythema migrans (EM) (not inevitable)
- Lymphocytoma, acrodermatitis chronica atrophicans
- Flu-like condition in the early stage even without EM as a sign of dissemination of the pathogens
- These are followed by (usually acute) manifestations in various organ and tissue systems with a wide variety of symptoms, see 2.4.
- Characteristic of the late manifestations are chronic fatigue and rapid fatiguability, an episodic disease course with a strong feeling of illness, and symptoms that appear in different places. In addition, many different symptoms of the organ manifestations concerned may also be present, see 2.4.

2.2 Diagnostic strategy

The following situations arise in daily practice:

- recent tick bite
- erythema migrans and lymphocytoma
- early stage without erythema migrans
- chronic stage.

2.2.1 Recent tick bite

Up to 50% of borreliosis patients deny having suffered a tick bite when their history is taken.[6/15/23/29/66/72/81/95/103/112/113/125/140] Therefore, a negative history of tick bites does not rule out Lyme borreliosis. It makes sense to examine the tick for Borrelia by PCR. However, a negative PCR result does not entirely rule out the infectiousness of the tick.[47]

The following principles therefore apply whenever a tick bite is present:

- observe the site of the bite for 4–6 weeks. If reddening occurs (erythema), consult the doctor immediately.
- serological testing to confirm insurance claims, for patients with a history of Lyme borreliosis and if it is planned to monitor the course of the disease.

If antibodies against Borrelia are found in the blood at a check-up examination 6 weeks after a tick bite, infection has occurred. (This can be proven only with a pair of sera). The longest latency period before the occurrence of symptoms of the disease was 8 years.[63/64]

2.2.2 Erythema migrans and lymphocytoma

Erythema migrans is evidential for Lyme borreliosis. Conclusion: immediate antibiotic treatment. The earlier the antibiotic treatment is started, the better the infection can be controlled. Therapeutic success is distinctly poorer even 4 weeks after the start of infection.[6]

Borrelia-specific antibodies do not appear until 2–6 weeks after the start of infection.[9/37/110/125/134] Antibiotic treatment at an early stage can prevent the development of antibodies, and therefore no seroconversion takes place. Seronegativity following early antibiotic treatment therefore does not rule out Lyme borreliosis in any way.

If there is a corresponding history (exposure to ticks) and a reddened nodular swelling is found, e. g. on the nipple, skin of the scrotum, bends of joints, and in children often on the external ear, this may be a lymphocytoma, which is evidential of Lyme borreliosis just as erythema migrans is, taking into consideration the differential diagnosis. A *Borrelia* lymphocytoma such as this, usually caused by Borrelia afzelii, also sometimes forms in the centre of an erythema migrans in the region of the original tick bite.

Borrelia can be isolated from all areas of an erythema migrans and of a *Borrelia* lymphocytoma.

2.2.3 Early stage without erythema migrans

Up to 50% of cases no EM is observed in the early stage of Lyme borreliosis, see 2.2.1. in the absence of EM, the diagnosis is based on the following criteria:

- circumstances of the illness: time spent in one's own garden and in the countryside, tick bite.
- thorough physical examination with inspection of the skin in the search for EM, including those possibly with diameters less than 5 cm[(155)] and lymphocytomas.
- laboratory diagnostic tests, see Table 2.

First manifestations of Lyme borreliosis sometimes do not occur for weeks to years after the start of infection.[(134)] If appropriate symptoms are present, especially if tick bites are mentioned during history-taking, or if there is a high risk of infection, Lyme borreliosis must always be considered in the differential diagnosis. For example, the following may occur in the early stage:

- transient migratory arthritis, arthralgia and myalgia
- bursitis, enthesitis
- headaches
- radicular pain syndromes (known as Bannwarth's syndrome)
- cranial nerve symptoms (especially facial nerve paresis)
- sensitivity disturbance
- cardiac dysrhythmias, stimulus formation and stimulus conduction disorders
- ocular symptoms (e. g. double vision).

2.2.4 Chronic stage

The time differentiation between the early and late stages is arbitrary. Disease manifestations of Lyme borreliosis which occur more than 6 months after the start of infection are designated in this Guideline as late manifestations or as chronic.

Lyme borreliosis can lead to numerous symptoms. The following are particularly frequent:

- fatigue (exhaustion, a chronic feeling of illness)
- encephalopathy (impaired cerebral function)
- muscular and skeletal symptoms
- neurological symptoms (including polyneuropathy)
- gastrointestinal symptoms
- urogenital symptoms
- ocular symptoms
- cutaneous symptoms
- heart diseases.

A cutaneous manifestation indicative of the illness in its late stage is acrodermatitis chronica atrophicans (ACA). Chronic polyneuropathy, which often accompanies ACA, is also seen as a typical manifestation of the illness in its late stage.

2.3 Occupational disease and accident insurance

Lyme borreliosis is classed as an occupational disease according to No. 3102 in Annex 1 to the Occupational Diseases Regulation [Berufskrankheiten-Verordnung (BKV)]. The only deciding factor is whether the accident suffered (tick bite), i. e. the infection, occurred in the course of one's work. For certain occupational groups at high risk of infection (including farmers and forestry workers, veterinarians), a relationship between the accident (tick bite) and the disease is generally accepted (causal relationship). For other occupational groups, this causal relationship must be demonstrated by the person affected.

Therefore, when a tick bite occurs during one's work and when manifestations of the illness subsequently appear, the attending physician must carefully document the history, the examination findings and the laboratory results. The same applies to a tick bite suffered by individuals who have taken out the relevant accident insurance.

In the case of a tick bite during work or suffered by those with accident insurance, a serological test for Borrelia should be performed as soon as possible after exposure and the test system should be documented. Seroconversion, a significant rise in titre or an increase in the bands in the immunoblot in the course of four to six weeks must be regarded as proof of a Borrelia infection.

Patients themselves should keep a diary and record cutaneous changes photographically. If the tick is still present, it is advisable to keep it for later testing for *Borrelia* by PCR.

2.4 Symptoms of chronic Lyme borreliosis

The symptoms of chronic Lyme borreliosis develop either seamlessly from the early stage, or only after a symptomless interval of months to years, or may indeed develop from the outset as chronic Lyme borreliosis without patients being aware of an early stage.[6] The conclusion to draw from this is that chronic Lyme borreliosis may exist even in the absence of history of a tick bite and EM, if the circumstances of the illness, its manifestations, and the differential diagnostic analysis make this a reasonable assumption.

Inflammation of the knee joint (gonitis), after other causes have been excluded by differential diagnosis, is evidential of the late phase of chronic Lyme borreliosis.[137]

The spread of Borrelia in the body leads to multiorgan or systemic disease with an exceptionally wide variety of possible manifestations apart from the most common symptoms mentioned in paragraph 2.2.4, see e. g. the detailed description in (125) pp. 261–495 or (134/136) or (6/35/39/72/77/98/124/125/126/127/158) and, specifically in relation to

- neurological and mental diseases (1/10/16/41/45/48/56/57/58/69/109/141),
- hormonal, vegetative and immunological manifestations (2/50/54/75/100/129/149),
- diseases of the muscular and skeletal systems (70/104/130),
- cutaneous manifestations (4/5/11/49/111/153),
- cardiovascular symptoms (93/133),
- ocular manifestations (79/91/105/106/157/161),
- manifestations during pregnancy (97/114).

2.5 Laboratory diagnostics

LB-related laboratory diagnostic tests for Borrelia infection are indicated if there are symptoms or clinical findings present which are consistent with Lyme borreliosis.

Serological monitoring tests in order to assess the success of treatment are not useful in chronic Lyme borreliosis. The success of treatment must be assessed clinically.[156, S. 51]

2.5.1 Direct identification of *Borrelia*

Lyme borreliosis is an infectious disease. Applying strict scientific criteria (especially in scientific studies), only the detection of Borrelia in culture with identification of the causative agent by PCR is proof of a Borrelia infection.

The identification of Borrelia DNA by a polymerase chain reaction (PCR for Borrelia) is also of major relevance.[142] Although the sensitivity of this identification technique is poor, especially in the late manifestations of Lyme borreliosis, tests should nevertheless be conducted to identify the causative agent, e.g. in skin biopsy specimens when suspicious cutaneous changes are present, in other biopsy specimens and puncture specimens (e. g. in cases of joint inflammation) and in the CSF in cases of acute neuroborreliosis. Negative results do not rule out Lyme borreliosis.

2.5.2 Borrelia serology

Borrelia serology is the basic diagnostic tool to answer the question whether a *Borrelia* infection might be present.

The test systems on the market (ELISA, immunoblotting) are not standardised. Therefore, findings from different laboratories can be compared to only a limited degree. Testing for the presence of Borrelia-specific antibodies is possible only with an immunoblot. If a Borrelia infection is suspected, an IgG and IgM immunoblot for Borrelia should be carried out in all cases. The request note to the laboratory must therefore state the request for:

Borrelia serology inc. immunoblotting for Borrelia

In addition, the clinical diagnosis or suspected diagnosis (CD or SD) at least should be given: Lyme borreliosis.

The procedure recommended by the Robert Koch Institute (RKI) and prescribed by the Association of Health Insurance Funds [Kassenärztliche Vereinigung (KV)], to conduct immunoblotting as well as a confirmatory test only if the ELISA is abnormal (or other so-called exploratory tests) (a process known as stepwise diagnostics), must be rejected because this leads to serologically false-negative results in up to a further 15% of patients.[7/81/154] The reason for this is that the antigen spectrum present in the immunoblot (see Table 1) is usually not identical to that included in the (ELISA) exploratory test. An ELISA and an immunoblot for Borrelia are two different test methods which can yield differing results in the individual case, even though they correlate with each other to a high degree.[131]

Table 1: Borrelia antigens for the identification of antibodies against Borrelia in an immunoblot (Western blot), modified after (8).

Borrelia **proteinan-tigen**	**Antigen description of the antibodies**	**Specificity**	**Remarks**
p14,18		high	Mainly in cases of B. afzelii described as immunogenic.
p19	OspE	unknown	
p21	DbpA (Decorin binding protein A)	high	Binding to Decorin protein on the host cell. Decorin is located especially in the skin.
p22,23, 24,25	Osp C	high	Most important marker of the early IgM response. To date, 13 different OspC types have been described.
p26	OspF	unknown	
p29	OspD	high	
p31	OspA	high	Seven different OspA types are known. The OspA type determines the species.
p34	OspB (outer surface protein B)	high	Antibodies only appear late post-infection
p39	Borrelia membrane protein A (BMPA)	high	Antibodies usually appear early post-infection.
p41	Flagellin protein	unspecific	Cross-reactions with other spirochaetes and with flagellated bacteria. IgM antibodies appear first and very early.
p58		high	
p60	Hsp6	unspecific	Antibodies often also appear in other bacterial infections.
p66	Hs	unspecific	Antibodies common in bacterial infections
p75	Hsp (Heat Shock Protein)	unspecific	
p83/100		high	Antibodies usually only in the later stage of the infection
VlsE	Variable major protein (VMP)-like sequence expressed	high	IgG Ab are possible even in the early stage. VlsE is expressed by Borrelia only in the host.

A negative serological finding does not rule out Lyme borreliosis.[7/115/118/154] There may be a disease requiring treatment even without the detection of antibodies. (Causes: e. g. antibiotic treatment starting early but inadequate with immunodepressants, including cortisone, exhaustion of the immune system, masking of the causative agents, genetic disposition.)

A positive serological finding means that the patient has acquired a Borrelia infection at some point in time. With a single serological test it is not possible to decide whether this infection is active or latent; at best this can be decided by the attending physician on the

basis of its clinical development. It is not within the remit of a laboratory physician to evaluate a positive finding as a "serological relic" i.e. antibodies evidential of an earlier infection.

2.5.3 Examination of the CSF

Diagnostic testing of the CSF is indicated in cases of acute inflammation of the nervous system:

- meningitis, meningo-encephalitis, encephalomyelitis, acute encephalitis,
- acute meningoradiculitis (Bannwarth's syndrome),[88] Guillain-Barré syndrome,
- cerebral vasculitis, myelitis,
- neuritis of cranial nerves (especially facial nerve paresis),
- acute polyneuropathy.

Testing of the CSF is not indicated in the following disease states in relation to Lyme neuroborreliosis, because pathological results are not to be expected:

- encephalopathy in chronic Lyme borreliosis,
- chronic polyneuropathy in the late stage,[66]
- cerebro-organic psychosyndrome.[44/78/82/90]

Pleocytosis (cell count over 5/µL), elevated protein level and evidence of the intrathecal synthesis of Borrelia-specific antibodies (serum/CSF ratio) are indications of acute neuroborreliosis.

However, if the neuroborreliosis occurs very soon after Borrelia infection and with late manifestations, Borrelia-specific antibodies will be absent from both the serum and the CSF or will appear sooner in the CSF than in the serum and vice versa.

The detection of intrathecally formed Borrelia-specific antibodies in the CSF is only very rarely possible in cases of Lyme borreliosis with neurological involvement. If acute neuroborreliosis is suspected, the treatment should not be made dependent on the laboratory results.[123]

2.5.4 Cellular diagnostics, lymphocyte transformation test (LTT)

As the cellular immune response (lymphocytes, monocytes) follows a more rapid dynamic than the relatively sluggish serological formation of antibodies, a lymphocyte transformation test (LTT) is faster to provide an indication of an active infection.

The following arguments support the use of cellular immunological methods in the laboratory diagnosis of Lyme borreliosis:

1. The direct identification of the causative agent is proof of Lyme borreliosis. The sensitivity of the methods for the direct identification of Borrelia is technically inadequate at present for daily practice.

2. A positive serological finding is not evidence of active Lyme borreliosis. On the other hand, a negative serological finding does not rule it out, especially when there are early manifestations of Lyme borreliosis, see 2.5.2 penultimate paragraph.

3. If there is no positive result available from a Borrelia culture or PCR for Borrelia, an LTT for Borrelia can provide an indication whether active Lyme borreliosis is present.[9] A positive result from the LTT for Borrelia is suspicious, but not evidential of an active Borrelia infection.

4. The LTT for Borrelia is clearly positive even in the early stage of Borrelia infection (even if erythema migrans is present) and is generally negative or at least clearly regressive 4 to 6 weeks after the conclusion of successful antibiotic treatment.

The indications for an LTT for Borrelia are:

- evidence of an active Borrelia infection in
  - seropositive patients with ambiguous symptoms
  - a seronegative result or result assessed serologically as borderline in patients with a strong clinical suspicion of Lyme borreliosis
- to monitor therapy approx. 4–6 weeks after concluding a course of antibiotic treatment
- to monitor progress if there is a clinical suspicion of a recurrence of Lyme borreliosis
- a new infection.

Certain laboratories offer different methods for the detection of Borrelia-specific activation of T lymphocytes, such as the EliSpot-Test-Borrelia®, for example, to answer these questions. In these methods, the induction of cytokine synthesis is measured at the cellular level. Although the EliSpot is well-established in the diagnosis of infectious diseases (TB), its importance in the diagnosis of borreliosis has yet to be tested by appropriate techniques.

2.5.5 CD57+NK cells

According to Stricker and Winger,[145] CD57+NK cells are often markedly reduced in the blood of patients with chronic Lyme borreliosis. It is not possible to evaluate the CD57+ NK cells as a laboratory parameter in connection with Lyme borreliosis at present, on account of the insufficient data available.

For a summary of laboratory diagnostics see table 2.

Table 2: Summary of laboratory diagnostics

Stage	**Laboratory test**
Recent tick bite (with or without EM)	Serological tests in cases of: - occupational accident (e. g. farmers and forestry workers) - claims against appropriate accident insurance - to verify antibody status and as a starting value for documenting the course of the illness. Other laboratory tests (relative indication): PCR for Borrelia in the tick (optional). If positive: serological test to determine the starting value
Early stage (with or without EM)	Serological tests (relative indication if EM present): IgM Ab, IgG Ab (enzymatic immunoassay) IgM blot, IgG blot LTT for Borrelia (relative indication) Diagnostic testing of CSF if neurological symptoms present
Chronic Lyme borreliosis (late stage)	Serological tests: IgM Ab, IgG Ab (enzymatic immunoassay) IgM blot, IgG blot LTT for Borrelia Other tests: PCR for Borrelia, Borrelia culture, immunofluorescence microscopy
Acute Lyme neuroborreliosis, chronic encephalomyelitis, severe polyneuritis, meningoradiculitis, Guillain-Barré syndrome	Diagnostic testing of CSF (cell count, protein, albumin (disturbance of blood-brain barrier), intrathecally formed specific Ab, Western blot, comparison of Western blots for serum/CSF, oligoclonal bands)
Therapy monitoring (4–6 weeks after antibiotic treatment)	LTT for Borrelia
In the case of a tick bite or in the early stage, a check-up after six weeks is necessary irrespective of the initial serological finding.	
PCR for Borrelia should be carried out on all biopsy specimens and puncture specimens.	
If the success of antibiotic treatment is insufficient, LTT for Borrelia 4-6 weeks after the conclusion of a course of treatment.	

2.6 Other technical medical tests

If Lyme borreliosis is suspected, it may be necessary to consult a specialist first before conducting the planned antibiotic treatment. The following specialists may be consulted depending on the clinical manifestation:

Neurologists	(CCT, MRT, SPECT, EMG, ENG, EPs),
Rheumatologists	(Laboratory tests),
Ophthalmologists	(eyesight, fundus of the eye, visual field, documentation before and during treatment with hydroxychloroquine),
Specialists in internal medicine	(ECG, epigastric sonography, hormone status especially TSH, anti-TPO),
Cardiologists	(echocardiography, long-term ECG, exercise ECG),
Lung specialists	(lung function, spiroergometry),
ENT specialists	(diagnosis of dizziness, audiometry),
Urologists	
Dermatologists	

Single Photon Emission Computed Tomography (SPECT)[36] is not a routine diagnostic method on account of the radiation exposure. In the event of professional trade association proceedings or legal disputes with insurance companies, it may be worthwhile as a supplementary test in an individual case, because it can sometimes reveal considerable cerebral perfusion disturbance in Lyme borreliosis.

2.7 Co-infections

Other infections may be present simultaneously with Lyme borreliosis which may worsen the patient's condition synergistically. Accompanying infections of this sort are known as co-infections.

Co-infections can be transmitted by ticks or by other routes of infection,[71] see tables 3 and 4. By modulating the immune system, co-infections aggravate the severity of disease states and are regarded as a significant reason for resistance to therapy.[22/32/43/53/73/87/89/107/116/117/143/146/148/152/158/162]

Although Bartonella DNA has been found in ticks,[14/33] there is disagreement whether this leads to transmission with subsequent bartonellosis[12] according to (150) there is no indication of this. On the other hand, other authors (3/17) describe cases of transmission by ticks and other arthropods. In patients with diseases of the central nervous system, Bartonella henselae has been detected in the CSF even without cat-scratch disease preceding it.[43] Moreover, Bartonella henselae, like Borrelia burgdorferi, is able to provoke a multi-organ disease.[132]

3. Antibiotic treatment of Lyme borreliosis

With regard to the efficacy of antibiotic treatment of LB, two discoveries are of exceptional importance:

- Antibiotics are more effective in the early stage than in the late phase.[6]

- With any antibiotic, therapeutic success may be delayed or fail to materialise completely,[76/94/99/121] with the consequence that follow-up treatment is necessary, possibly with a different antibiotic.[31/159]

Table 3: Co-infections transmitted by ticks

Disease	Causative agent	Treatment
HGA (Human granulocytic anaplasmosis, formerly HGE = Human granulocytic ehrlichosis)	Anaplasma phagocytophilum	Doxycycline (also in children >8 years) Alternatives: rifampicin, levofloxacin (not yet unequivocally documented clinically)
Rickettsiosis	Rickettsia helvetica	Doxycycline
Mediterranean spotted fever	Rickettsia conorii	Doxycycline
Q fever	Coxiella burnetii (Transmission by the marsh tick Dermacentor reticulatus [a European hard tick], but mostly by inhalation or orally)	Doxycycline, macrolides, fluoroquinolones
Babesiosis	Babesia bovis (Switzerland) Babesia microti (Poland)	Atovaquone + azithromycin, quinidine + clindamycin
Bartonellosis	Bartonellae	Azithromycin, trimethoprim-sulfomethoxazole, ciprofloxacin, doxycycline, rifampicin

Table 4: Co-infections not transmitted by ticks

Disease	Causative agent	Treatment
mycoplasma infection	Species of the genera mycoplasmas and ureaplasma	Doxycycline, minocycline, azithromycin, clarithromycin, rifampicin (rifampicin always in combination!)
Chlamydia infection	Chlamydophila pneumoniae Chlamydia trachomatis	Doxycycline, minocycline, azithromycin, clarithromycin, cotrimoxazole, rifampicin
Yersiniosis	Yersinia enterocolitica (Y. pseudotuberculosis (USA))	Lactulose; antibiotics only by intricacies: Doxycycline, cotrimoxazole

The scientific basis for antibiotic treatment is still inadequate at the present time, with the exception of the localised early stages (EM). The considerable shortcomings in the scientific-clinical analysis are reflected in therapeutic guidelines, which are severely limited in the reliability of their recommendations and in their evidence base in the international literature,[159] and they do not meet the requirements from the medical and health-policy aspects.

Successful antibiotic treatment is possible only if the individual has an effective immune system. With regard to antibiotic treatment, problems also arise with Borrelia due to natural or acquired resistance. The causative agent of Lyme borreliosis can evade the immune system by what are known as “escape mechanisms”.[7/74]

In the early stage, i. e. in the first 4 weeks after the start of infection, a failure rate of 10% is to be expected with antibiotic treatment.[121/135] In the chronic forms, it is significantly higher at up to 50%.[30/31/52/55/74/99/121] Even earlier studies referred to the problem area of chronic Lyme borreliosis and the limits of its susceptibility to treatment.[31/55/59/61/62/65/92/94/121/138] In all these studies, the duration of treatment was generally limited to a maximum of four weeks. Considerable therapeutic failure rates occurred under these conditions, even with repeated courses of treatment.[78/82/90] The duration of treatment is of decisive importance for the success of antibiotic treatment.

There are now a few studies available which provide evidence of the positive effect and the safety of long-term antibiotic therapy.[25/26/27/30/36/44/46/51/52/81/144]

The limited effect of antibiotic treatment is documented in numerous studies: Pathogens were cultured even after supposedly highly effective antibiotic therapy.[63/74/81/96/119/120/122/139/147] For example, Borrelia were isolated from the skin after multiple courses of antibiotic treatment (ceftriaxone, doxycycline, cefotaxime).[40/61/76/81/122/147] A discrepancy was also found between the antibiotic sensitivity of Borrelia in vitro versus in vivo.[74] Moreover, additional factors are involved in vivo which lie in the capability of Borrelia to evade the immune system,[60/83/85/86/120] specifically under the influence of various antibiotics.[80]

Hypothetically, the persistence of Borrelia is attributed to its residency within the cell and to the development of biologically less active permanent forms (sphaeroplasts, encystment) among other things.[19/85/86/94/120] In addition, Borrelia was also shown to develop biofilms with the effect of resisting complement and typical shedding (casting off antibodies from the surface of the bacterium).[83/85/86] Other mechanisms, too, e. g. diversification, i. e. changing protein antigens located on the membrane, the loss of plasmids and processes to inactivate complement,[85/86/120] promote the “escape mechanism”, i. e. the capability of the pathogen to evade the immune system, that has also been demonstrated in other bacteria. The ability of the pathogen to down-regulate proteins (pore-forming protein) might also diminish the antibiotic effect.[34/74/84]

There are four randomised studies relating to the therapy of chronic Lyme borreliosis,[44/78/82/90] in which different antibiotics were compared when used in the antibiotic treatment of encephalopathy. It was shown in these studies that the cephalosporins were superior to penicillin.[31/62/94/96] Doxycycline in its customary dosage resulted in only relatively low serum levels and tissue concentrations, whereas the concentrations in the case of the cephalosporins were markedly higher, i. e. with regard to the minimum inhibitory concentration (MIC) the values with the cephalosporins were at least ten times higher than with doxycycline.[63]

A wide therapeutic spectrum and a high tissue concentration of antibiotic is necessary in tissue with a poor blood supply (connective tissue, structures such as the skin, joint capsules, fasciae, tendons), as Borrelia have a particular affinity to these sorts of tissue.[42/108]

Of the available antibiotics, tetracyclines, macrolides and betalactams have proved effective in the treatment of Lyme borreliosis. The efficacy of other antibiotics, especially the carbapenems, telithromycin and tigecycline, is based on in vitro studies.[20/74/160] There are no clinical studies except for imipenem, which was given a favourable clinical assessment.[64]

The treatment of Lyme borreliosis can be conducted either as a monotherapy[159] or with a synchronous combined therapy.

The efficiency of a combined antibiotic therapy has not been scientifically attested to date; this form of treatment is based on microbiological findings and on empirical data that have not so far been systematically investigated.

3.1 Unsuitable antibiotics

The following antibiotics are not suitable for the treatment of Lyme borreliosis:

- carboxypenicillins
- acylaminopenicillins (supposedly effective; no clinical experience; usually employed in the treatment of inpatients)
- first generation cephalosporins (cefazolin, cefotoxitin)
- oral first and second generation cephalosporins, except for cefuroxime axetil
- quinolones
- aminoglycosides
- chloramphenicol
- clindamycin
- glycopeptide antibiotics
- folate antagonists (except for trimethoprim according to Gasser[51])
- cotrimoxazole
- atovaquone
- nitrofurans
- erythromycin[151]

3.2 Suitable antibiotics

The antibiotics effective against Borrelia are listed in table 5 with particulars of their properties.

As table 5 shows, only the substances metronidazole and hydroxychloroquine have an effect on encysted forms.[101] Hydroxychloroquine also has an effect on mobile Borrelia. This does not apply to metronidazole.[18/19] Hydroxychloroquine assists the action of macrolides[19] and possibly also that of the tetracyclines.

Table 5: Effective antibiotics in Lyme borreliosis

Antibiotic	Effective intra-cellularly	Enters the CSF	Effective against encysted forms	Plasma half-life
Betalactams				
Ceftriaxone	—	(+)*	—	8 hrs
Cefotaxime	—	(+)*	—	1 hr
Cefuroxime axetil	—	—	—	1 hr
Benzathine benzylpenicillin	—	+	—	3 days
Phenoxymethyl penicillin	—	—	—	30 min
Amoxicillin	—	—	—	1 hr
Tetracyclines and glycylcyclines				
Doxycycline	+	14%	—	15 hrs
Minocycline	+	40%	—	15 hrs
Macrolides**				
Clarithromycin	+	5%	—	4 hrs
Azithromycin	+	—	—	68 hrs tissue half-life
Nitroimidazoles				
Metronidazole	+	+	+	7 hrs
Co-drugs				
Hydroxychloroquine	+	+	+	30-60 days tissue half-life

* The betalactams have a poor ability to enter the CSF but, on account of their wide therapeutic spectrum, attain concentrations in the CSF which are clearly above the minimum inhibitory concentration (MIC).[74]

** Macrolides are not used in cases of QTc intervals (frequency-corrected QT intervals) of more than 440 milliseconds with heart rates between 60 and 100 bpm.[67,68]

3.2.1 Monotherapy

Antibiotic treatment should be adjusted for weight as a matter of principle. This is particularly applicable in the case of children and patients with above or below normal weight.

Some physicians of the German Borreliosis Society are critical of the use of 3rd generation cephalosporins or of penicillins alone in Lyme borreliosis, because they may possibly favour the intracellular residency of Borrelia and its encystment.(101/120)

Checks of blood count (white cells, red cells, platelets), GPT, lipase, creatinine, possibly prothrombin time and PTT are required weekly at first, and subsequently every 2-3 weeks. If ceftriaxone is used, a sonographic check every 3 weeks is necessary to rule out sludge formation in the gall bladder. When macrolides are used, ECG checks must be carried out at fortnightly intervals.

Table 6: Antibiotic monotherapy of Lyme borreliosis

In the early stage (localised)	
Doxycycline	400 mg daily (children of 9 years old and above)
Azithromycin	500 mg daily on only 3 or 4 days/week
Amoxicillin (pregnant women, children)	3000-6000 mg/day
Cefuroxime axetil	2 × 500 mg daily
Clarithromycin	500-1000 mg daily
Duration dependent on clinical progress at least 4 weeks. If ineffective with regard to EM maximum 2 weeks; then change antibiotic.	
In the early stage with dissemination and late stage	
Ceftriaxone	2 g daily
Cefotaxime	2-3 x 4 g
Minocycline	200 mg daily, introduced gradually
Duration dependent on clinical progress. If ineffective, change antibiotic, at the earliest after 4 weeks.	
Alternatives in the late stage	
Benzathine benzylpenicillin	1.2 Mega 2x / week or 2 x 1.2 Mega 1x / week
Metronidazole	400-1200 mg daily, whenever possible parenterally 6-7 days, max. 10 days, also repeatedly in particular well-fonded cases

Treatment with 3rd generation cephalosporins is worthwhile in the form of pulsed therapy after initial continuous therapy. In the pulsed phase the drugs are used on 3-4 days a week.(61)

A summary of antibiotic monotherapy will be given in table 6.

The danger of a Jarisch-Herxheimer reaction must be borne in mind with any antibiotic treatment of Lyme borreliosis, irrespective of the stage. Corticosteroids should be administered parenterally only in an emergency, depending on the severity of the reaction.

During long-term antibiotic treatment, probiotic treatment should be given to protect the intestinal flora and to support the immune system (e. g. E. coli strain Nissle 1917, lactobacillus, bifidobacterium etc.). Several meta-analyses show that the prophylactic use of probiotics lowers the risk of antibiotic-associated diarrhoea.[13/24/28/38/102/127] If diarrhoea occurs that is not readily brought under control (e. g. with Saccharomyces boulardii), the antibiotic treatment should be discontinued immediately and a check should be carried out in particular to establish if an infection with Clostridium difficile toxin A/B is present. If mycoses occur[128] e. g. in the gastro-intestinal tract, non-systemic antimycotic treatment should be given, in parallel with the antibiotics, intermittently or continuously, and continued for up to 2 weeks beyond the antibiotic treatment.

3.2.2 Combined therapy

In a combined therapy, two, or sometimes three, antibiotics are used at the same time, usually in the form of synchronously combined long-term antibiotic treatment,[146] see table 7.

The action of macrolides and possibly also of tetracyclines is intensified by the simultaneous administration of hydroxychloroquine, which, like metronidazole, acts on encysted forms of Borrelia.[36]

Third-generation cephalosporins can be combined with minocycline (enters the CSF) alternating between the two, i. e. each substance alone on 3 days a week each. Both can be combined with hydroxychloroquine. Hydroxychloroquine can be tested for tolerability e. g. given as a single drug within the first 3 days of therapy. The dosage of minocycline should be increased gradually. If minocycline is not tolerated, it can be replaced with doxycycline or clarithromycin.

Doxycycline and minocycline can be combined with azithromycin and hydroxychloroquine. To make it easier to identify drug intolerance, the treatment should not be started with the individual antibiotics given simultaneously. It is preferable to add the other antibiotics staggered over time, say at intervals of one to two weeks.

3.3 Prevention

As Lyme borreliosis is overwhelmingly transmitted in Europe by Ixodes ricinus (the European castor bean tick), the preventive measures described below relate to this vector.

Prevention involves the following factors:

- exposure to ticks
- protective clothing
- repellents
- examination of the skin after exposure
- removal of ticks that have started feeding.

Table 7: Antibiotics for a combined therapy of Lyme borreliosis

Betalactams	
Ceftriaxone	2 g daily
Cefotaxime	3 x 4 g daily
Tetracyclines	
Minocycline*	200 mg daily
Doxycycline	400 mg daily
Macrolides	
Azithromycin	500 mg daily on 3 or 4 days / week
Clarithromycin	2 x 500 mg daily
Others	
Metronidazole	400-1200 mg daily, whenever possible parenterally, 6-7 days, max. 10 days, also repeatedly in particular well-fonded cases
Hydroxychloroquine	200 mg daily or every other day (cumulative)
Duration in the late and disseminated early stage: 3 months and more. Recurrence is treated again as necessary, but generally in cycles of shorter treatment times, e. g. 3 days - 3 weeks. *Take special note of particulars of risks with minocycline!	

With regard to the risk of exposure, it should be noted that ticks wait in grasses and undergrowth up to a height of 120 cm above the ground. On contact, the ticks are brushed off the vegetation and can get to all parts of the body across the skin (beneath clothing). Ticks prefer moist and warm areas of skin, but a tick bite can basically occur on any part of the body. A particular risk arises also from contact with wild animals and with domesticated animals which are exposed to ticks periodically.

The following main sources of risk emerge from this constellation:

- private gardens
- grass, low undergrowth and similar vegetation
- spending time in the countryside
- domesticated animals, e. g. horses, dogs, cats
- wild animals.

Protective clothing should prevent ticks gaining entry, especially on the arms and legs, by having tight-fitting cuffs. The simplest way in some cases is to tuck one's trousers into one's socks.

There is special protective clothing available and various repellents which reduce the risk by being applied directly onto the skin or clothing before exposure. However, the repellents are not completely effective and their duration of action is limited to a few hours.

After exposure, i. e. after spending time in the countryside for example, one should examine one's body for ticks.

The problem with this is that the early stages of the adult ticks, the larvae and nymphs, are only 1 mm in size at best and are therefore easy to miss.

A tick that has started feeding must be removed as soon as possible because the risk of infection increases with the length of time spent feeding. Fine-pointed tweezers or a tick removal tool are suitable for removing a tick. After grasping it with the tweezers, the tick is pulled slowly and steadily out of the skin. The site of the bite should then be disinfected.

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The first version of these recommendations for the diagnosis and treatment of Lyme borreliosis was written in 2007/2008 by the German Borreliosis Society [(Deutsche Borreliose-Gesellschaft (DBG)]. The recommendations were revised in 2009/2010 by a working party. This was followed by a repeated, anonymous consultation process in which all ordinary members of the Society and external experts were able to submit, comment and vote on suggested amendments. The resulting document was finally discussed in 2010 at the Annual Congress of the DBG and approved on 24th November 2010 by its members.

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Potential conflicts of interest
The authors are physicians with their own practices, working for a medical laboratory, a clinic or are in retirement. Furthermore there are no economic interests which are significant for the work on these guidelines. There are no political, academic (e. g. membership of specific "schools") or scientific conflicts of interest, too.