

LYME BORRELIOSIS  
Principles of clinical diagnosis



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# Introduction

- **Lyme borreliosis is a disease,** manifested by symptoms and signs
- infection (serum antibodies)  $\neq$  illness
- USA  $\neq$  Europe
- 90% vs  $\leq$  50% symptomatic infections
- clinical definitions helpful for diagnosis



# Introduction

- Lyme borreliosis is a disease, manifested by symptoms and signs
- infection (serum antibodies) ≠ illness
- USA ≠ Europe
- 90% vs <50% symptomatic infections
- clinical definitions helpful for diagnosis



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# Diagnosing LB

## Case definitions/guidelines

**CDC:** *Case definition 2011*

**IDSA:** *Clinical practice guidelines. Clin Infect Dis 2006*

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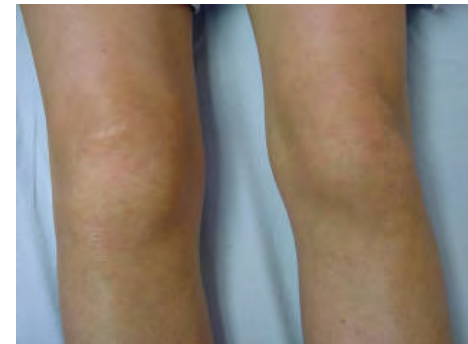
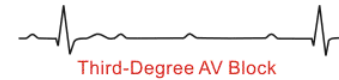
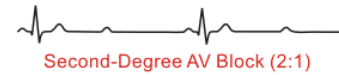
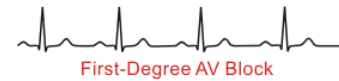
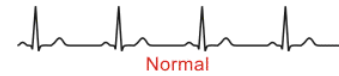
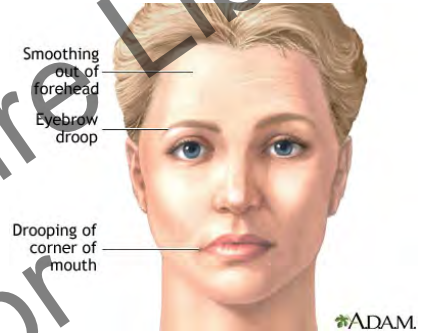
**EUCALB:** *Clinical case definitions for Lyme borreliosis. Wien Klin Wochenschr 1996*

**ESCMID:** *Guidelines for the diagnosis of tick-borne bacterial diseases in Europe. Clin Microbiol Infect 2004*

**Stanek et al.** *Lyme borreliosis: Clinical case definitions for diagnosis and management in Europe. Clin Microbiol Infect 2011*

**national**

# Clinical manifestations



ESCMID Online Lecture Library  
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# LB manifestations in adults

## Skin involvement

Erythema migrans

Borrelial lymphocytoma

Acrodermatitis chronica  
atrophicans

Manifestation	Number (%)
Erythema migrans	621 (83.4)
Borrelial lymphocytoma	4 (0.5)
Lyme neuroborreliosis	48 (6.4)
Lyme carditis	2 (0.3)
Lyme arthritis	21 (2.8)
Acroder.chr.atr.	49 (6.6)
$\Sigma$	745

Data from UMC 2000 Ljubljana, Slovenia





# Diagnosis of Lyme borreliosis

Recognition of a clinical manifestation

+

Demonstration of borrelial etiology of this  
manifestation



# Diagnosis of Lyme borreliosis

Recognition of a clinical manifestation

+

Demonstration of borrelial etiology

- direct demonstration of infection-most reliable
- serology
  - indicates contact with Lyme borreliae
  - symptomatic vs asymptomatic infection?
  - recent infection vs infection in the past?
  - active infection vs status post infection?

# Clinical diagnosis

→ Typical skin manifestations:

**Erythema migrans**

Borrelial lymphocytoma

Acrodermatitis chronica atrophicans

→ Meningoradiculoneuritis (Bannwarth sy)

# Clinical diagnosis

## Typical skin manifestations:

### **Erythema migrans**

Borrelial lymphocytoma

Acrodermatitis chronica atrophicans

## Meningoradiculoneuritis (Bannwarth sy)

Signs of involvement of: nervous system

joints

heart

eyes

## Principles:

- search for the presence of “typical signs” of LB
- demonstration of borrelial infection of the involved organ
- demonstration of borrelial infection with serum antibodies
- search for and exclusion of other reasons



# Clinical diagnosis

## Typical skin manifestations:

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- caution

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- caution

# Clinical diagnosis

## Principles:

- search for the presence of “typical signs” of Lyme
- demonstration of borrelial infection of the involved organ

## In CNS involvement:

- isolation of Borreliae from CSF - rarely
- demonstration of borrelial genetic material in CSF by PCR
- demonstration of intrathecal production of borrelial antibodies

# Clinical diagnosis

## Principles:

- search for the presence of “typical signs” of Lyme
- demonstration of borrelial infection of the involved organ

## In arthritis:

- (intraarticular production of borrelial antibodies)
- isolation of *Borreliae* from joint fluid/synovia – rarely
- PCR of joint fluid or of synovia



# Clinical diagnosis

## Principles:

- search for the presence of “typical signs” of LB
- demonstration of borrelial infection of the involved organ

## In heart involvement:

- demonstration of *Borrelia* in heart (biopsy)

## In eye involvement:

- demonstration of intraocular borrelial antibody production

Search for other explanations for the involvement.



# Clinical diagnosis

## Typical skin manifestations:

### **Erythema migrans**

Borrelial lymphocytoma

Acrodermatitis chronica atrophicans

### Meningoradiculoneuritis (Bannwarth sy)

## Unusual signs of Lyme borreliosis

### Principles:

- search for the presence of “typical signs” of LB
- demonstration of borrelial infection of the involved organ
- demonstration of borrelial infection with serum antibodies
- search for and exclusion of other reasons
- caution!

# Clinical diagnosis

## Typical skin manifestations:

### **Erythema migrans**

Borrelial lymphocytoma

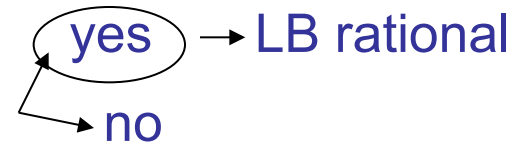
Acrodermatitis chronica atrophicans

Meningoradiculoneuritis (Bannwarth sy)

## Symptoms (without objective signs)

## Principles:

- search for the presence of “typical signs” of LB



- demonstration of borrelial infection of the involved organ

- demonstration of borrelial infection with serum antibodies

- search for and exclusion of other reasons

- caution!

# Clinical diagnosis

## Typical skin manifestations:

### **Erythema migrans**

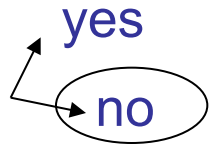
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## Symptoms (without objective signs)

### Principles:

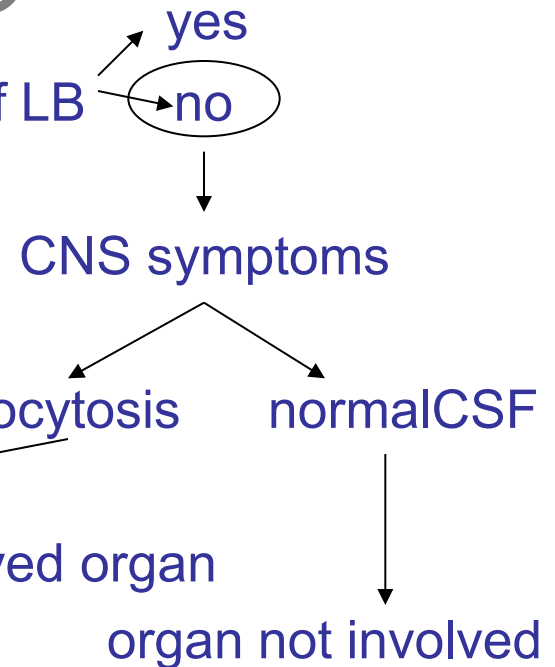
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# Clinical diagnosis

## Symptoms (without objective signs)

### Principles:

- search for the presence of “typical signs” of LB



- demonstration of borrelial infection of the involved organ

# Clinical diagnosis

## Typical skin manifestations:

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- search for and exclusion of other reasons
- **caution!**



# Erythema migrans - clinical characteristics

- expanding red, or bluish-red patch  $\geq 5$  cm
- central clearing +or-



- systemic symptoms Europe: 20-51%, USA: 69-80%



# Different case definitions for EM

+ parameter required; – parameter not required; \* criterion required only for lesions <5 cm;

Requirements	Definitions				
	Slovenian Strle 1996	EUCALB Stanek 1996	ESCMID Brouqui 2004	CDC 2011	ESCMID Stanek 2011
Expansion	+	+	+	+	+
Central clearing	+ (often)	+ (often)	+ (often)	+ (often)	-
Diameter ≥5 cm	+	+ (most cases)	-	+	+
Additional systemic symptoms	-	+ (may be present)	-	+ (most patients)	-
Tick bite	+*	+ (exposure to ticks)	+ (minor criterium)	-	+*
Delay in appearance	+*	-	-	-	+*
Delay in appearance >2 days	-	-	-	-	+*



# Borrelial lymphocytoma



- painless bluish-red nodule/plaque (85 patients):
  - breast 80%
  - ear lobe, helix 9%
  - other 11%

- Concomitant EM 79%
- Seropositive 35% (IFT)
- Borrelia isolated in 11/46 (24%)
- Histology in unclear cases



Maraspin et al. Wien Klin Wochenschr 2002

# Acrodermatitis chronica atrophicans



- red or bluish-red lesions
- insidious onset
- acral parts, extensor surface
- initially swelling
- atrophy: violaceous, thin, wrinkling skin
- mono/polyneuropathy

# Acrodermatitis chronica atrophicans



- red or bluish-red lesions
- insidious onset
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- initially swelling
- atrophy: violaceous, thin, wrinkling skin
- mono/polyneuropathy

Establishment of borrelial infection:

- Seropositive ~ 100%
- Histology: supporting
- Borrelia isolated in ~ 1/3

# Lyme neuroborreliosis

- mainly lymphocytic meningitis, meningoradiculitis, cranial nerve, peripheral nerve involvement
- rarely encephalitis, myelitis, encephalopathy

# Lyme neuroborreliosis

- meningoradiculitis, severe pain, worse at night
- meningitis, protracted course
- cranial nerve, PFP in 80%
- peripheral nerve involvement, in ACA
- encephalopathy, rare

# Lyme neuroborreliosis

- Clinical presentation of meningitis, meningoradiculitis, nerve involvement
- +
- Lymphocytic pleocytosis
- +
- Seroconversion of Bb antibodies
- Bb detected in CSF by culture or PCR
- Intrathecal specific antibody synthesis
- Recent or concomitant EM

# Lyme neuroborreliosis

- meningitis, meningoradiculitis,  
nerve involvement
- encephalitis, myelitis
- +
- Lymphocytic pleocytosis
- +

## ➤ Seroconversion of Bb antibodies

- Bb detected in CSF by culture or PCR
- Intrathecal specific antibody synthesis
- Recent or concomitant EM
  - usually not a useful criterion, the majority of patients are seropositive
  - confirms recent borrelial infection, does not confirm CNS involvement





# Lyme neuroborreliosis

- meningitis, meningoradiculitis,  
nerve involvement

- encephalitis, myelitis

+

- Lymphocytic pleocytosis

+

- Seroconversion of Bb antibodies

➤ **Bb detected in CSF by culture or PCR**

- Intrathecal specific antibody synthesis

- Recent or concomitant EM

- isolation of Bb from CSF is a low-yield procedure,  
results obtainable only after several weeks

- PCR in CSF has low sensitivity, false-positive  
findings, lacks procedure standardization

# Lyme neuroborreliosis

- meningitis, meningoradiculitis,  
nerve involvement

- encephalitis, myelitis

+

- Lymphocytic pleocytosis

+

- Seroconversion of Bb antibodies

- Bb detected in CSF by culture or PCR

## ➤ Intrathecal specific antibody synthesis

- Recent or concomitant EM

➤ generally used for establishment of LNB

➤ insensitive during the first few weeks of CNS involvement, long persistence of the antibodies



# Lyme neuroborreliosis

- meningitis, meningoradiculitis,  
nerve involvement

- encephalitis, myelitis

+

- Lymphocytic pleocytosis

+

- Seroconversion of Bb antibodies

- Bb detected in CSF by culture or PCR

- Intrathecal specific antibody synthesis

## ➤ Recent or concomitant EM

➤ clinical evidence supporting diagnosis of LNB

# Lyme arthritis

Intermittent course 85% → knee 27/28

Later chronic 6%

Unremitting 9%

shoulder, ankle, elbow, TMJ,

wrist, hip 28-43%

RIF, DIF, MCP, MTP 11%

Steere et al. Ann Intern Med 1987

Monoarticular 60%

Oligoarticular 32%

Polyarticular 6%

Herzer. Scand J Infect Dis 1991



Asymmetric, acute, effusion, warm skin of normal colour.

# Lyme arthritis

- Recurring course for several years
- Chronic arthritis in 10%

+

Lab: ESR, CRP n/↑

Synovial fluid: L 10-35 (range 0.5-110)x10<sup>9</sup>, PMN 70-80%, protein↑

Rtg: nonspecific, erosions in chronic arthritis

+

## ➤ Bb antibodies in serum

- Bb detected in synovial fluid/tissue by culture or PCR
- Recent or concomitant EM or neuro disorder
  - does not guarantee that the infection is active
  - or that it is located in the joints
  - does not suggest Lyme arthritis

# Lyme arthritis

- Recurring course for several years
- Chronic arthritis in 10%

+

Lab: ESR, CRP n/↑

Synovial fluid: L 10-35 (range 0.5-110)x10<sup>9</sup>, PMN 70-80%, protein↑

Rtg: nonspecific, erosions in chronic arthritis

+

- Bb antibodies in serum

➤ **Bb detected in synovial fluid/tissue by culture or PCR**

- Recent or concomitant EM or neuro disorder

➤ low success rate of culture

➤ sensitivity of PCR ~ 85%

# Lyme arthritis

- Recurring course for several years
- Chronic arthritis in 10%

+

Lab: ESR, CRP n/↑

Synovial fluid: L 10-35 (range 0.5-110)x10<sup>9</sup>, PMN 70-80%, protein↑

Rtg: nonspecific, erosions in chronic arthritis

+

- Bb antibodies in serum
- Bb detected in synovial fluid/tissue by culture or PCR

➤ **Recent or concomitant EM or LNB or ACA**

➤ clinical evidence supporting diagnosis of Lyme arthritis

# Lyme carditis

- conduction disturbances → AV block
- myo/pericardial involvement → ST, T wave, cardiomegaly, LV dysfunction, acute heart failure
- chronic cardiomyopathy???



# Lyme carditis

- conduction disturbances → AV block
- myo/pericardial involvement → EKG, echo, MRI, biopsy
- +
  - exclusion of other explanations
  - +
    - Bb antibodies in serum
    - Bb detected in endomyocardial biopsy
    - Recent or concomitant EM or neuro disorder

# Lyme carditis

- conduction disturbances → AV block
  - myo/pericardial involvement → ST, T wave, cardiomegaly, LV dysfunction, acute heart failure
- +

## ➤ Bb detected in endomyocardial biopsy

- Bb antibodies in serum
- Recent or concomitant EM or neuro disorder
  - endomyocardial biopsy not a routine diagnostic procedure
  - the potential yield is suboptimal due to the focality of myocarditis
  - the procedure is risky

# Lyme carditis

- conduction disturbances → AV block
- myo/pericardial involvement → ST, T wave, cardiomegaly, LV dysfunction, acute heart failure
- +
  - Bb detected in endomyocardial biopsy
- **Bb antibodies in serum**
- Recent or concomitant EM or neuro disorder
  - the majority of patients are seropositive
  - seroconversion does not confirm heart involvement
  - seropositivity: recent vs delayed?  
active vs past infection?

# Lyme carditis

- conduction disturbances → AV block
- myo/pericardial involvement → ST, T wave, cardiomegaly, LV dysfunction, acute heart failure
- +
- Bb antibodies in serum
- Bb detected in endomyocardial biopsy

## ➤ Recent or concomitant EM or LNB

- EM in up to 85% of Lyme carditis cases

# Ocular involvement

Eyes rarely affected:

I (inflammation): conjunctivitis, uveitis, papillitis, episcleritis, keratitis

II (extraocular LB manifestations): palsy due to involvement of VII, III, IV, VI, orbital myositis

# Ocular involvement

conjunctivitis, uveitis, papillitis, episcleritis, keratitis

+

## ➤ Bb antibodies in serum

- Intraocular borrelial antibodies synthesis
- Bb detected in ocular fluid
- Recent or concomitant LB manifestations
  - reports of eye involvement, doubtful meaning

# Ocular involvement

conjunctivitis, uveitis, papillitis, episcleritis, keratitis

+

- Bb antibodies in serum

## ➤ Intraocular borrelial antibodies synthesis

- Bb detected in ocular fluid

- Recent or concomitant LB manifestations

➤ eye puncture is not a routine procedure

➤ the volume of ocular fluid is small



# Ocular involvement

conjunctivitis, uveitis, papillitis, episcleritis, keratitis

+

- Bb antibodies in serum

- Intraocular borrelial antibodies synthesis

➤ **Bb detected in ocular fluid**

- Recent or concomitant LB manifestations

➤ isolation of borrelia from eye tissue reported once

➤ borrelial DNA found in eye structures. However, several patients with positive PCR were seronegative, critical interpretation needed





# Ocular involvement

conjunctivitis, uveitis, papillitis, episcleritis, keratitis

+

- Bb antibodies in serum
- Intraocular borrelial antibodies synthesis
- Bb detected in ocular fluid

➤ **Recent or concomitant LB manifestations**

- most reliable method in practice



# Conclusion

**Diagnosis of LB is based on two cornerstones:**

- Recognition of clinical manifestation/s and
- Demonstration of borrelial etiology of the manifestation/s

**TABLE 1. Summary of clinical case definitions for Lyme borreliosis**

Term	Clinical case definition	Laboratory evidence: essential	Laboratory/clinical evidence: supporting
Erythema migrans	Expanding red or bluish-red patch ( $\geq 5$ cm in diameter) <sup>a</sup> , with or without central clearing. Advancing edge typically distinct, often intensely coloured, not markedly elevated.	None	Detection of <i>Borrelia burgdorferi</i> s.l. by culture and/or PCR from skin biopsy.
Borrelial lymphocytoma (rare)	Painless bluish-red nodule or plaque, usually on ear lobe, ear helix, nipple or scrotum; more frequent in children (especially on ear) than in adults.	Seroconversion or positive serology <sup>b</sup> Histology in unclear cases	Histology. Detection of <i>B. burgdorferi</i> s.l. by culture and/or PCR from skin biopsy. Recent or concomitant EM.
Acrodermatitis chronica atrophicans	Long-standing red or bluish-red lesions, usually on the extensor surfaces of extremities. Initial doughy swelling. Lesions eventually become atrophic. Possible skin induration and fibroid nodules over bony prominences.	High level of specific serum IgG antibodies	Histology. Detection of <i>B. burgdorferi</i> s.l. by culture and/or PCR from skin biopsy.
Lyme neuroborreliosis	In adults mainly meningo-radculitis, meningitis; rarely encephalitis, myelitis, very rarely cerebral vasculitis. In children mainly meningitis and facial palsy.	Placytosis and demonstration of intrathecal specific antibody synthesis <sup>c</sup>	Detection of <i>B. burgdorferi</i> s.l. by culture and/or PCR from CSF. Intrathecal synthesis of total IgM, and/or IgG and/or IgA. Specific serum antibodies. Recent or concomitant EM.
Lyme arthritis	Recurrent attacks or persisting objective joint swelling in one or a few large joints. Alternative explanations must be excluded.	Specific serum IgG antibodies, usually in high concentrations	Synovial fluid analysis. Detection of <i>B. burgdorferi</i> s.l. by PCR and/or culture from synovial fluid and/or tissue.
Lyme carditis (rare)	Acute onset of atrio-ventricular (I-III) conduction disturbances, rhythm disturbances, sometimes myocarditis or pancarditis. Alternative explanations must be excluded	Specific serum antibodies	Detection of <i>B. burgdorferi</i> s.l. by culture and/or PCR from endomyocardial biopsy. Recent or concomitant erythema migrans and/or neurologic disorders.
Ocular manifestations (rare)	Conjunctivitis, uveitis, papillitis, episcleritis, keratitis.	Specific serum antibodies	Recent or concomitant Lyme borreliosis manifestations. Detection of <i>B. burgdorferi</i> s.l. by culture and/or PCR from ocular fluid.

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

<sup>b</sup>as a rule, initial and follow up samples have to be tested in parallel in order to avoid changes by inter-assay variation.

<sup>c</sup>In early cases intrathecally produced specific antibodies may still be absent.