LYME BORRELIOsis: MYTHS OR REALITIES

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ISP-WIV 27 nov 2014
"Extensive and often inaccurate publicity about the risk and the outcome of Lyme Borreliosis has produced considerable anxiety about the disease. One result of the reaction is the inappropriate use of serological testing for Lyme Borreliosis to identify the cause of widely prevalent, non specific symptoms, such as pain and fatigue. This practice, in tum, has led to a virtual epidemic of overdiagnosis and overtreatment of patient which only serves to perpetuate the myth that Lyme disease is commonly associated with severe, long-term morbidity".

U. Hengge (Lancet Inf Dis 2003)
## Lyme Borreliosis: Myths or Realities?

<table>
<thead>
<tr>
<th>Myth</th>
<th>Fact</th>
</tr>
</thead>
<tbody>
<tr>
<td>No accurate tests</td>
<td>There are no tests available to prove that the organism is eradicated or that the patient is cured.</td>
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<tr>
<td>Fewer than 50% of patients with Lyme disease recall a tick bite.</td>
<td>Fewer than 50% of patients with Lyme disease recall any rash.</td>
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<tr>
<td>The ELISA screening test is unreliable.</td>
<td>Up to fifty percent of ticks in Lyme-endemic areas are infected.</td>
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<tr>
<td>The common ELISA test you receive at your doctor's office misses 35% of culture proven Lyme disease. Some studies indicate up to 50% of the patients tested for Lyme disease receive false negative results.</td>
<td>The onset of Lyme disease symptoms can be easily mistaken for other illnesses. Once symptoms are more evident the disease may have already entered the central nervous system, and could be hard to cure.</td>
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<tr>
<td>40% of Lyme patients end up with long term health problems.</td>
<td>Short treatment courses have resulted in upwards of a 40% relapse rate, especially if treatment is delayed.</td>
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<tr>
<td>The average patient sees 5 doctors over nearly 2 years before being diagnosed.</td>
<td>There has never been a study demonstrating that 30 days of antibiotic treatment cures chronic Lyme disease. However there is much documentation demonstrating that short courses of antibiotic treatment fail to eradicate the Lyme spirochete.</td>
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</tbody>
</table>
ECOLOGY AND TRANSMISSION

- The most common tick-born disease in Europe (US)
  - *Ixodes ricinus*… *I. persulcatus*
  - Main reservoir: small rodents and some birds
  - ≈2-4 years, **4-stage** life cycle: eggs, larva, **nymphs**, **adults**

- Nymphs mainly responsible for transmission from spring to autumn

- Mean prevalence of infected ticks in Europe: ≈13%
  - Less in nymphs (≈10%) vs **adults** (≈18%)
  - Highest rates: Eastern Europe

- Others pathogens: *Anaplasma*, *Rickettsia* sp., *Babesia* sp., *Coxiella burnetii*, *Francisella tularensis*: rare !!
At least 19 genospecies of *Borrelia*

- **US:** *B. burgdorferi* ss, **Europe:** *B. afzelii, B. garinii* ... *B. burgdorferi* ss
- Correlation between genospecies and clinical manifestations
  - All: Erythema migrans
  - *B. afzelii* = cutaneous, *B. garinii* = CNS, *B. burgdorferi* ss = articular and CNS
EPIDEMIOLOGIC DATA FROM BELGIUM

In Belgium, 3 different data sources:

- **Sentinel Laboratory Network** (since 1991)
- **Sentinel General Practitioner Network**
- **Minimal Clinical Dataset from hospital recording** (ICD9)
  - Report the number of hospitalizations for LB.

These data are complementary, allow to describe a trend but not an exhaustive number of cases.
Follow-up of the number of positive serological tests performed by sentinel laboratories between 1993 and 2014 in Belgium, WIV-ISP.
Number of **positive serological tests** performed between 1993 and 2014 **by administrative zone** in Belgium, WIV-ISP

**Per age-group (/ 100,000) study period 2003-2014**
Number of consultations for asymptomatic bites and erythema migrans, by 10,000 patients, for period 2003-2004 and 2008-2009, Sentinel general practitioner network, Belgium, WIV-ISP

<table>
<thead>
<tr>
<th>Time period</th>
<th>Asymptomatic tick bites</th>
<th>Erythema migrans</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Incidence per 10,000 patients (95%)</td>
<td>Incidence per 10,000 patients (95%)</td>
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<tr>
<td>2003-2004</td>
<td>18.59 (17.16-20.02)</td>
<td>8.32 (7.36-9.27)</td>
</tr>
<tr>
<td>2008-2009</td>
<td>18.65 (17.29-20.08)</td>
<td>9.02 (8.08-10.03)</td>
</tr>
<tr>
<td>pvalue</td>
<td>not significant</td>
<td>not significant</td>
</tr>
</tbody>
</table>

Number of hospitalization for Lyme borreliosis (ICD9) in Belgium, 1999-2010
CLINICAL MANIFESTATIONS

• In our European area, a large proportion of patients exposed to Borrelia will never develop any clinical disease.

• Take into account the risk of tick bite rather than a documented bite (tick bites are not noticed in > 50% of symptomatic patients with LB)

• An hypersensitivity reaction at the bite (<5cm) within the few days ≠ Erythema migrans

• Clinical manifestations of LB can be divided in 3 phases (with possible overlaps):
  • Early localized disease
  • Early disseminated disease
  • Late disease
**CLINICAL MANIFESTATIONS**

**EARLY LOCALIZED LB (DAYS-WEEKS)**

**Erythema Migrans:** >90% of clinical manifestations LB (Central Europe)
- *expanding* erythematous skin lesion at the site of the tick bite
- >3-30 days (typically 7-14d) and 5-75 cm (M=15cm)
- Erythema or target lesion, sometimes necrotic or vesicular in the center, usually asymptomatic
- Systemic symptoms (20-30%): fever, myalgia, arthralgia, malaise
- Disappears even when untreated

**Lymphocytoma** (~2%)
- 1-6 months after the tick bite, mostly in children
- Painless bluish-red nodule, usually on the ear (nipples, scrotum).
CLINICAL MANIFESTATIONS

EARLY DISSEMINATED LB (DAYS-WEEKS)

Appear within weeks or few months after the tick bite

Multiple EM (20-30% of EM)
- systemic symptoms are common
  - Other lesions may be less than 5 cm but expanding!

Acute Neuroborreliosis (3-15% of clinical manifestations of LB)
- Children: mainly facial palsy with or without aseptic meningitis
- Adults: mainly meningo-radiculitis (up to 85%) with radicular pain or motor/sensitive deficits
- Rare: encephalitis, isolated aseptic meningitis, other cranial nerve palsies, ...

Carditis (<1-2%): fluctuating degrees of atrio-ventricular block,
- frequent spontaneous resolution but may required temporary pacing
- Very rare reports of myocarditis, pericarditis

Arthritis
CLINICAL MANIFESTATIONS

LATE DISSEMINATED LB (MONTHS-YEARS)

- **Arthritis** (≈5%)
  - The most common manifestation of late Borrelia infection
  - US >> Europe
  - Asymetric, 1-2 larger joint(s) with almost invariably the knee
  - Recurrent or persistant joint swelling
  - 25,000 WC/mm³ (500-110,000) with polymorphonuclear predominance

- **Acrodermatitis chronica atrophicans** (≈1-2%)
  - Only in adults and mainly in Europe
  - Long-standing bluish-red lesions, most often on the extremities, up to 10 years after infection
  - Can be associated with peripheric neuropathy
CLINICAL MANIFESTATIONS
LATE DISSEMINATED LB (MONTHS-YEARS)

- **Late neuroborreliosis**
  - very rare <5% neurological manifestations!
  - Slowly progressive encephalomyelitis or radiculomyelitis with ataxia, spastic paraparesia, ...
  - Always more than 6 months of evolution
  - Cerebral CT/RMN and Lumbar puncture always pathologic

*No scientific evidence* of relation with fibromyalgia, psychiatric or behavioral disorders, neurological degenerative diseases...
LYME BORRELIOSIS DIAGNOSIS

**Culture as a (old) gold standard**
- Specificity but very low sensitivity and very fastidious

**Serology as the mainstay of lab diagnosis**
- **Enzyme immuno Assay 2\(^{nd}\) or 3\(^{rd}\) generation**
  - Ig G Specificity 80 up to 95%, lower in IgM
  - IgG sensitivity: mean 80%, depending of the stage of the disease
    - \(\approx 50\%\) erythema migrans (few weeks after tick bite)
    - \(\approx 100\%\) after 6 weeks (without early AB treatment or severe immunosuppression)
  - Cross reaction: Treponema (Syphilis), Leptospira, Rickettsia, Babesia, auto-immune diseases, CMV, EBV (IgM), …
DIAGNOSIS
Two-tiered serological testing as gold standard serologic diagnosis of seropositivity

Two-Tiered Testing for Lyme Disease

First Test
- Enzyme Immunoassay (EIA)
  - OR
  - Immunofluorescence Assay (IFA)

Second Test
- Signs or symptoms
- IgM and IgG Western Blot
- IgG Western Blot

Consider alternative diagnosis
OR
If patient with signs/symptoms consistent with Lyme disease for ≥ 30 days
obtaining a convalescent serum

- Western blot
  Specificity ≈ 95% = confirmation test
  Variation in interpretation and in the products
LYME BORRELIOSIS DIAGNOSIS

- **Serology:**
  - Antibodies persist for years, even after treatment
  - No indication of serologic follow up
  - Serology to be performed **only** if suggestive symptoms and exposition: **antibodies not indicative of active disease**
  - Routine serologic testing of persons bitten by ticks not useful

- **PCR:** low sensitivity (20-30%) excepted in arthritis (60-80%)

- **Biopsy:** Lymphocytoma, ACA or atypical EM

- **Others:** **not shown reliable**!
  - urinary antigen, lymphocytes transformation tests, cytokines production: **lower sensitivity and specificity**

**NEW** BLOOD TEST: ELISPOT AND CD57+ AT INTERNATIONAL STANDARDS
**DIAGNOSIS**

**SUSPECTED NEUROBORRELIOSIS**

- **Serology** can be negative in the early phase (80% sensitivity)
  - Always + after 6 weeks from bite or symptoms

- **Lumbar Puncture !**
  - Pleiocytosis (10-1000/mm³) *with lymphocytosis*
  - Mild proteinorachy
  - Index of antibodies in CSF/serum
    - ! May persists for years after infection in CSF

- Clinical diagnosis (without LP) **only when** associated with others manifestations (EM) or bilateral palsy in children
# Diagnosis Performance

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Ab Sensitivity</th>
<th>Other Testings</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema migrans</td>
<td>38-88%</td>
<td>(atypical) PCR</td>
<td>60-80%</td>
</tr>
<tr>
<td></td>
<td>&gt;6w: 100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocytoma</td>
<td>70%</td>
<td>Histopath</td>
<td>100%</td>
</tr>
<tr>
<td>Early LNB</td>
<td>80%</td>
<td>Intrathecal Ab CSF pleocytosis</td>
<td>55-80%</td>
</tr>
<tr>
<td></td>
<td>&gt;6w: 100%</td>
<td>CSF PCR</td>
<td>95-100%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10-50%</td>
</tr>
<tr>
<td>Late LNB</td>
<td>100%</td>
<td>Intrathecal Ab CSF pleocytosis</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>Arthritis</td>
<td>100%</td>
<td>Synovial fluid PCR</td>
<td>46-88%</td>
</tr>
<tr>
<td>Carditis</td>
<td>80-100%</td>
<td>ECG</td>
<td></td>
</tr>
<tr>
<td>ACA</td>
<td>100%</td>
<td>Histopath PCR</td>
<td>68-90%</td>
</tr>
</tbody>
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LYME BORRELIOSIS TREATMENT

PRINCIPLES

• All clinical manifestations have to be treated

• Lack of rapid improvement and/or resolution of clinical symptoms despite administration of appropriate antibiotic therapy should make questioning the diagnosis

• Prolonged therapy or association of medications are not indicated, not proven more effective while being potentially toxic
### Lyme Borreliosis Treatment Basics

**Erythema Migrans**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Adult Dosage</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st choice: Doxycycline</td>
<td>200mg/d in one or 2 doses (CI in pregnant woman or child &lt; 8 years)</td>
<td>10 days</td>
</tr>
<tr>
<td>2nd choice: Amoxicillin</td>
<td>500mg 3x/d</td>
<td>14 days</td>
</tr>
<tr>
<td>3rd choice: Cefuroxime-axetil</td>
<td>500 mg 2x/d</td>
<td>14 days</td>
</tr>
<tr>
<td>4th choice: Macrolides</td>
<td>azithromycin 1g then 500 mg/d for 4 days or 500 mg/d for 7 days clarithromycin 500 mg 2x/d</td>
<td>5-7 days 14 days</td>
</tr>
</tbody>
</table>

**Acute Neuroborreliosis**

<table>
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<th>Antibiotic</th>
<th>Adult Dosage</th>
<th>Duration</th>
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<tbody>
<tr>
<td>Doxycycline</td>
<td>200mg/d in 1 or 2 doses</td>
<td>14 days</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>2g 1x/d</td>
<td>14 days</td>
</tr>
<tr>
<td>Penicilline G</td>
<td>3-4 Miu 6x/j</td>
<td>14 days</td>
</tr>
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**Arthritis**

<table>
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<tr>
<th>Antibiotic</th>
<th>Adult Dosage</th>
<th>Duration</th>
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<tbody>
<tr>
<td>Doxycycline</td>
<td>200mg/d in 1 à 2 doses</td>
<td>30 days</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>500mg 3x/d</td>
<td>30 days</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>2g 1x/d</td>
<td>14 days</td>
</tr>
</tbody>
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POST-TREATMENT SYMPTOMS
POST-LYME BORRELIOSIS SYNDROM

• Objective manifestations typically improve/resolve during or after completion of therapy

• **10-15% patients: long-term aspecific symptoms (>6m)**
  • Fatigue, musculo-skeletal pain, difficulties of concentration, …
  • If severe enough to be disabling: « Post-Lyme syndrome »
    • Entity still debated
  • No evidence of benefit of repeated antibiotic treatment
  • Alternative multidisciplinary approaches
PREVENTION

Antibiotic prophylaxis after tick bite

- Not recommended
- Less than 1% of tick-bite will give disease
- Mainly due to nymphs (not recognized)
1. Clinical manifestations of LB have to be treated
2. More accurate epidemiological data would be useful
3. EM is a clinical diagnosis
4. Most serologic testings are performed in a nonspecific presentation → overdiagnosis due to antibodies seroprevalence
5. In early phase, serology can be negative but >6 weeks IgG are present
6. Diagnosis of acute neuroborreliosis require LP, unless specific manifestations
7. Treatment are reliable but prolonged/repeated therapies or association are not effective and potentially toxic.
SHARKS!!!
...aren't you scared??

...oh this is nothing, you should try Lyme disease!