Lyme disease

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Tick vectors:

*B. burgdorferi* is transmitted to humans by ticks of the *ixodes recinus* complex.
Should antibiotic therapy be given after a tick bite to prevent infection?

- **Single-dose doxycycline prophylaxis recommended if:**
  - *Ixodes* adult or nymph has been attached for ≥36 h
  - Prophylaxis can be provided ≤72 h of tick removal
  - Local rate of *B. burgdorferi* infection in ticks >20%
  - Doxycycline can be used

- **Efficacy of prophylaxis unknown in children >8 y (don’t use doxycycline for children ≤8 y)**

- **Alternative: watch for EM, other signs of infection**
  - Initiate treatment if they develop Lyme disease
  - Outcomes excellent if treated during early EM stage
What symptoms and signs should prompt investigation for Lyme disease?

- **Risk factor for tick exposure**
  - Living in or frequenting endemic areas

- **Symptoms consistent with Lyme disease**
  - Fever, fatigue and/or malaise, headache, arthralgia, myalgia, articular articular inflammatory arthritis
  - Erythema migrans
  - Carditis
  - Peripheral neuropathy
  - Encephalomyelitis

- **Many people are unaware of having been bitten**
**Early localized disease**
- 3-30 days after tick exposure
- Characterized by EM at the site of the tick bite
- Acute localized disease with systemic symptoms

**Early disseminated disease**
- Days after original EM lesion to a month after tick exposure
- Bacteria travel bloodstream to sites distant original EM
- Secondary EM, acute carditis, nervous system symptoms, articular arthritis

**Late disseminated Lyme disease**
- Months to years after the original tick exposure
- Joint and/or nervous system symptoms
- Other systemic symptoms are usually not present
- **Differentiation in manifestations according to subspecies** (B. garinii infection associated with neurologic disease, B. afzelii with acrodermatitis,...)
Clinical stages of Lyme disease

- **Stage I (Rash)**
- **Stage II (Early neurologic)**
- **Stage III (Late neurologic)**

Timeline:
- Months
- Years
Clinical stages of Lyme disease

1. Early localised infection (stage 1 or primary Lyme borreliosis): erythema migrans with locoregional lymphadenopathy, rarely Borrelia lymphocytoma
Clinical stages of Lyme disease

1. Early localised infection (stage 1 or primary Lyme borreliosis): erythema migrans with locoregional lymphadenopathy, rarely Borrelia lymphocytoma

2. Early disseminated infection (stage 2 or secondary Lyme borreliosis): multiple erythema migrans, early neuroborreliosis, carditis, arthritis, ocular manifestations, facial nerve palsy, ...

3. Late disseminated infection (stage 3 or tertiary Lyme): acrodermatitis atrophicans (Pick Herxheimer), arthritis, late neuroborreliosis, ...
What are the major complications of Lyme disease, how often do they occur, and how should they be diagnosed?

- **Major manifestations usually resolve over time**
  - EM, facial palsy, heart block, arthritis
  - Recovery typically complete except for nerve palsies and radiculopathy
  - Antibiotic therapy speeds resolution of some symptoms (arthritis, cardiac conduction delay), not all (facial palsy)
  - Treatment in early stages of disease generally results in excellent outcomes with minimal sequelae

- **Serologic testing used to assess probability of Lyme disease as cause of these symptoms (exception: EM)**
What diagnostic tests should be done to confirm Lyme disease and other tick-borne diseases?

**Testing is not always warranted**
- Do not test if patients in endemic areas and potentially exposed to ticks present with EM: treat with antibiotics
- Do not test if patients in endemic areas have no history of tick exposure or only nonspecific symptoms
- High incidence of false+ results associated with testing

**Current testing recommendation is 2-step approach**
- Initial screening with ELISA
- If positive, follow with supplemental Western blot test
- Both tests can identify either IgM or IgG antibodies
Diagnostic tests

- Clinical and epidemiological context dominant
- Serology important in later stages of illness
- IgM interpretable within 6-8 weeks after exposure
- Enzyme-immunoassay (EIA) and immunoblot standard in which 3 generations
  - 1st generation sonicate of B burgdorferi sensu lato and intact bacteria: false positive reactions
  - 2nd generation: less aspecific reactions
  - 3rd generation: specific recombinant antigens of B b s.l or synthetic peptide C6
  - Specificity IgG 80-95%; sensitivity in Europe lower
  - Higher specificity immunoblot
- LTT: not standardized and validated for B burgdorferi and consequently not recommended
- PCR: tool in diagnosis of cutaneous and articular manifestations
- PCR: low value in neurologic disease (sensitivity 10-50%); no clear value for blood, serum or plasma
Interpretation of serology

- Seroprevalence of Borrelia may increase up to 50% in certain regions or groups (job or leisure in nature)

- To avoid serology in absence of specific clinical signs (e.g. persistent fatigue, aspecific diffuse longstanding pain,...)

- Prolonged positive serology, even after antibiotherapy, without indication for control (no parameter of illness activity); cave overinterpretation of serology in general

- Reinfection possible: IgG↑ in association with manifestations of Lyme borreliosis
Interpretation of serology

- Erythema migrans: clinical diagnosis; no indication of serological confirmation (sensitivity IgG and IgM ± 50%; 70% of followup after 4 weeks); abortive response after antibiotherapy

- When in doubt: skin biopsy with suggestive APD

- Borrelia lymfocytoma: serology often positive; sensitivity 70% and with negative initial result seroconversion in the short term; skin biopsy only in case of uncertain diagnosis; PCR sensitivity 67%

- Early neuroborreliosis: IgM/IgG generally positive; within 3 weeks 21%, after 6 weeks 90%; until 98% at control at least 4 weeks after 1st serology
Interpretation Borrelia serology

- **CSF:** pleiocytosis (lymphocytosis) + moderate ↑ lymphocytosis + CSF index + limited sensitivity of PCR on CSF (10-50 %)

- **Carditis:** generally pos serology (> 80 %) with high IgG titers

- **Lyme arthritis:** always pos serology with high IgG; PCR on joint fluid

- **Late neuroborreliosis:** always pos serology on blood; CSF + medical imaging always abnormal

- **ACA:** always pos serology with high IgG + specific APD
What antibiotic treatment should be given? For how long?

- Efficacy equal: penicillins, tetracyclines, some 2\textsuperscript{nd} and 3\textsuperscript{rd} generation cephalosporins
  - Macrolides may be less efficacious
  - Doxycycline has best bioavailability, CNS penetration
  - Minocycline also good oral bioavailability, CNS penetration but associated with vestibular side effects

- Consider stage of disease and organs involved
  - Determines oral vs parenteral therapy
  - Determines treatment duration
Localized disease: oral antibiotics (i.e., doxycycline 100 mg orally twice daily for 10-21 days)

Early disseminated disease (mild carditis, isolated facial nerve palsy): extend oral regimen to 21-28 days

Higher degree heart block or meningitis: parenteral therapy with ceftriaxone 2 g IV once daily

Severe neurologic disease: full course of parenteral therapy

Late-stage arthritis: oral antibiotics for 28 days; consider second course (oral or parenteral) if arthritis continues

Pregnant women: don’t use doxycycline

Children: use adjusted dosages and don’t use doxycycline if younger than 8 y old
Consider classical syndromes as key for a diagnosis of Lyme

However, take atypical presentations into account and a (restrictive interpretation of) a grey zone, certainly in combination with a positive serology

Emphasize the reliability of conventional serology and avoid the trap of sophistic reasoning/thought, typical for the chronic Lyme hype

Consider in the grey zone a single classic treatment schedule/regimen for Lyme with maximum 1 month of doxycycline or ceftriaxone

Avoid non-contributory/unhelpful discussions on the interpretation of negative vs positive serology/PCR/LTT

Avoid the trap of following patient expectations in the sympathetic mode; stay empathic but true to evidence based medicine
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4. “Chronic” Lyme disease, “post Lyme syndrome”
What is "chronic Lyme disease," and how should it be treated?

- Continuation of symptoms after antibiotic therapy
  - Fatigue, myalgia, arthralgia, memory loss, headache
  - Long-term fibromyalgia- or chronic fatigue-like symptoms
  - Highly controversial whether legitimate clinical entity
  - Symptoms may occur at same rate as in general population

- Current recommendation for management of chronic disease: supportive care only
“Chronic Lyme disease” distinguished from well-accepted Lyme disease sequelae

- Little disagreement some manifestations persist after antibiotic therapy
- Arthritis, neuropathy, radiculopathy
- Can be documented objectively through medical testing
- Persistent arthritis after antibiotic therapy often responds to anti-inflammatory or immunomodulatory agents

Possible mechanisms for persistent manifestations

- Preexisting damage from inflammatory response to infection
- Persistent low-level infection
- Autoimmune response
Definition of “chronic Lyme disease”

- Not clearly defined, controversial entity or concept
- Terminology to be avoided?
- “Post Lyme syndrome”
  - Aspecific symptoms, occurring after adequate antimicrobial treatment of a patient with correct initial diagnosis: fatigue, musculoskeletal pain, concentration and memory problems, headache, …
  - Terminology proposed for patients, in whom symptoms persist/are present for at least 6 months
### Figure 1. The Four Predominant Categories of Disease Associated with Chronic Lyme Disease.

Only patients with category 4 disease have post–Lyme disease symptoms.

<table>
<thead>
<tr>
<th>Category 1</th>
<th>Category 2</th>
<th>Category 3</th>
<th>Category 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms of unknown cause, with no evidence of <em>Borrelia burgdorferi</em> infection</td>
<td>A well-defined illness unrelated to <em>B. burgdorferi</em> infection</td>
<td>Symptoms of unknown cause, with antibodies against <em>B. burgdorferi</em> but no history of objective clinical findings that are consistent with Lyme disease</td>
<td>Post–Lyme disease syndrome</td>
</tr>
</tbody>
</table>

Table 3. Evidence against Active Infection in Patients with Subjective Symptoms Persisting for More Than 6 Months after Antibiotic Treatment for Lyme Disease.

**Signs and symptoms**
Absence of concomitant objective clinical signs of either disease or inflammation and no progression to objective signs or development of inflammation\(^{29,32}\)

Similar symptoms common in persons who have never had Lyme disease\(^{24,25,30,31,48}\)

**Laboratory tests**
Persistence of symptoms independently of persistent seropositivity\(^{20,29,32,47}\)
Absence of either positive cultures or positive polymerase-chain-reaction results from clinical specimens\(^{32,40}\)

**Treatment**
No substantive response to antibiotic therapy in controlled treatment trials\(^{32-34}\)

No documented resistance of *Borrelia burgdorferi* to recommended antibiotics\(^2\)

Absence of recognized risks for failure of antibiotic therapy; these include host immunodeficiency or an infection in which there is local ischemia, a foreign body (biofilm), a sequestrum, or an abscess\(^2\)

**Other evidence**
Certain studies in animals\(^2\)
Lack of precedent for the use of long-term antibiotic treatment in other spirochetal infections\(^{23,49}\)

PLEASE study: randomized trial of longer term therapy for symptoms attributed to Lyme disease

- Double-blind, placebo controlled RCT, Europe

- Aim: assessment of long term vs short term antimicrobial treatment on outcome/persistent symptoms after classic Lyme or in unexplained symptoms + positive Borrelia burgdorferi IgG or IgM

- No baseline difference between groups
- Significant functional impact (low SF36)

End of treatment period
(P > 0.05 among groups)
### Table 2. Treatment Effect at the End of the Treatment Period in the Modified Intention-to-Treat Population.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Doxycycline Group (N = 86)</th>
<th>Clarithromycin-Hydroxychloroquine Group (N = 96)</th>
<th>Placebo Group (N = 98)</th>
<th>P Value(^{†})</th>
<th>Doxycycline Group vs. Placebo Group</th>
<th>Clarithromycin-Hydroxychloroquine Group vs. Placebo Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome: SF-36 physical-component summary(§)</td>
<td>35.0 (33.5 to 36.5)</td>
<td>35.6 (34.2 to 37.1)</td>
<td>34.8 (33.4 to 36.2)</td>
<td>0.69</td>
<td>0.2 (-2.4 to 2.8)</td>
<td>0.9 (-1.6 to 3.3)</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAND SF-36(§)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental-component summary</td>
<td>40.2 (38.6 to 41.9)</td>
<td>40.5 (38.9 to 42.1)</td>
<td>40.1 (38.6 to 41.7)</td>
<td>0.94</td>
<td>0.1 (-2.7 to 2.9)</td>
<td>0.4 (-2.3 to 3.1)</td>
</tr>
<tr>
<td>Global-health composite</td>
<td>36.1 (34.5 to 37.8)</td>
<td>36.6 (35.1 to 38.1)</td>
<td>36.0 (34.5 to 37.5)</td>
<td>0.85</td>
<td>0.1 (-2.6 to 2.9)</td>
<td>0.6 (-2.1 to 3.2)</td>
</tr>
<tr>
<td>Physical-functioning scale</td>
<td>41.9 (40.5 to 43.3)</td>
<td>42.1 (40.8 to 43.4)</td>
<td>41.0 (39.7 to 42.3)</td>
<td>0.44</td>
<td>0.9 (-1.4 to 3.2)</td>
<td>1.1 (-1.1 to 3.4)</td>
</tr>
<tr>
<td>Role-physical scale</td>
<td>33.6 (31.6 to 35.6)</td>
<td>34.4 (32.5 to 36.3)</td>
<td>33.9 (32.0 to 35.8)</td>
<td>0.84</td>
<td>-0.3 (-3.7 to 3.1)</td>
<td>0.5 (-2.8 to 3.8)</td>
</tr>
<tr>
<td>Bodily pain scale</td>
<td>39.1 (37.5 to 40.7)</td>
<td>40.5 (39.0 to 41.9)</td>
<td>39.4 (37.9 to 40.9)</td>
<td>0.42</td>
<td>0.3 (-2.9 to 2.4)</td>
<td>1.1 (-1.5 to 3.6)</td>
</tr>
<tr>
<td>General-health scale</td>
<td>37.1 (35.6 to 38.6)</td>
<td>38.4 (37.0 to 39.8)</td>
<td>37.5 (36.2 to 38.9)</td>
<td>0.41</td>
<td>0.4 (-2.9 to 2.0)</td>
<td>0.9 (-1.5 to 3.3)</td>
</tr>
<tr>
<td>Mental-health scale</td>
<td>45.1 (43.8 to 46.4)</td>
<td>45.2 (43.9 to 46.4)</td>
<td>45.1 (43.9 to 46.4)</td>
<td>1.00</td>
<td>-0.4 (-2.3 to 2.2)</td>
<td>0.0 (-2.1 to 2.2)</td>
</tr>
<tr>
<td>Role-emotional scale</td>
<td>44.7 (42.4 to 47.0)</td>
<td>41.4 (39.2 to 43.6)</td>
<td>42.6 (40.4 to 44.8)</td>
<td>0.11</td>
<td>2.1 (-1.7 to 6.0)</td>
<td>-1.2 (-5.0 to 2.6)</td>
</tr>
<tr>
<td>Social-functioning scale</td>
<td>36.3 (34.2 to 38.4)</td>
<td>38.5 (36.6 to 40.5)</td>
<td>37.5 (35.6 to 39.5)</td>
<td>0.32</td>
<td>1.2 (-4.7 to 2.3)</td>
<td>1.0 (-2.4 to 4.4)</td>
</tr>
<tr>
<td>Vitality scale</td>
<td>42.5 (40.9 to 44.0)</td>
<td>42.4 (41.0 to 43.9)</td>
<td>41.9 (40.5 to 43.4)</td>
<td>0.85</td>
<td>0.5 (-2.0 to 3.1)</td>
<td>0.5 (-2.0 to 3.0)</td>
</tr>
<tr>
<td>Checklist Individual Strength(¶)</td>
<td>88.7 (84.4 to 92.9)</td>
<td>87.1 (83.0 to 91.1)</td>
<td>88.4 (84.4 to 92.4)</td>
<td>0.84</td>
<td>0.3 (-6.9 to 7.4)</td>
<td>-1.3 (-8.3 to 5.6)</td>
</tr>
<tr>
<td>Fatigue-severity scale</td>
<td>39.4 (37.3 to 41.5)</td>
<td>38.6 (36.6 to 40.5)</td>
<td>38.3 (36.3 to 40.2)</td>
<td>0.73</td>
<td>1.1 (-2.4 to 4.6)</td>
<td>0.3 (-3.1 to 3.7)</td>
</tr>
</tbody>
</table>

* All study groups first received a 2-week course of ceftriaxone before the randomized 12-week course of study drug or placebo. P values were derived by analysis of covariance. All scores are adjusted for sex and baseline SF-36 physical-component summary score.
† Bonferroni correction was used for pairwise comparisons among the three study groups.
‡ Group differences should exceed 2 to 4 T-points (exact number of points varies for each scale) to indicate minimally important differences on all RAND SF-36 scales.\(^{14}\)
§ The ranges of the RAND SF-36 scores were as follows: RAND SF-36 physical-component summary, 15 to 61; mental-component summary, 11 to 66; global-health composite, 8 to 65; physical-functioning scale, 16 to 58; role-physical scale, 20 to 60; general-health scale, 20 to 64; mental-health scale, 16 to 66; role-emotional scale, 19 to 54; social-functioning scale, 12 to 57; and vitality scale, 26 to 70. For all scales, higher scores indicate better quality of life.
¶ Scores on the Checklist Individual Strength range from 20 to 140 for the total score and from 8 to 56 for the fatigue-severity scale. For both scales, higher scores indicate more fatigue.
No proof that vague/aspecific symptoms occur more frequently in this patient group as compared with the general population.

No known physiopathological mechanism that may explain this entity. Different possibilities have been dismissed (auto-immunity, disturbed cytokine production, impaired host defense, ...) hitherto without clear conclusions.

**Benefit of longstanding or repeated antibiotic therapy not proven.** Unnecessary exposure of the patient to possible toxicity, side effects and development of resistant bacteria.
Affirmatory reassurance on the basis of a solid general internal medicine assessment

Offering of an alternative explanatory model, with the advice to abandon the unhelpful search and fixation of/on a pure and simple biologic explanation

Try to facilitate a bridge towards a biopsychosocial model of care
Werkgroep:

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