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Lyme disease

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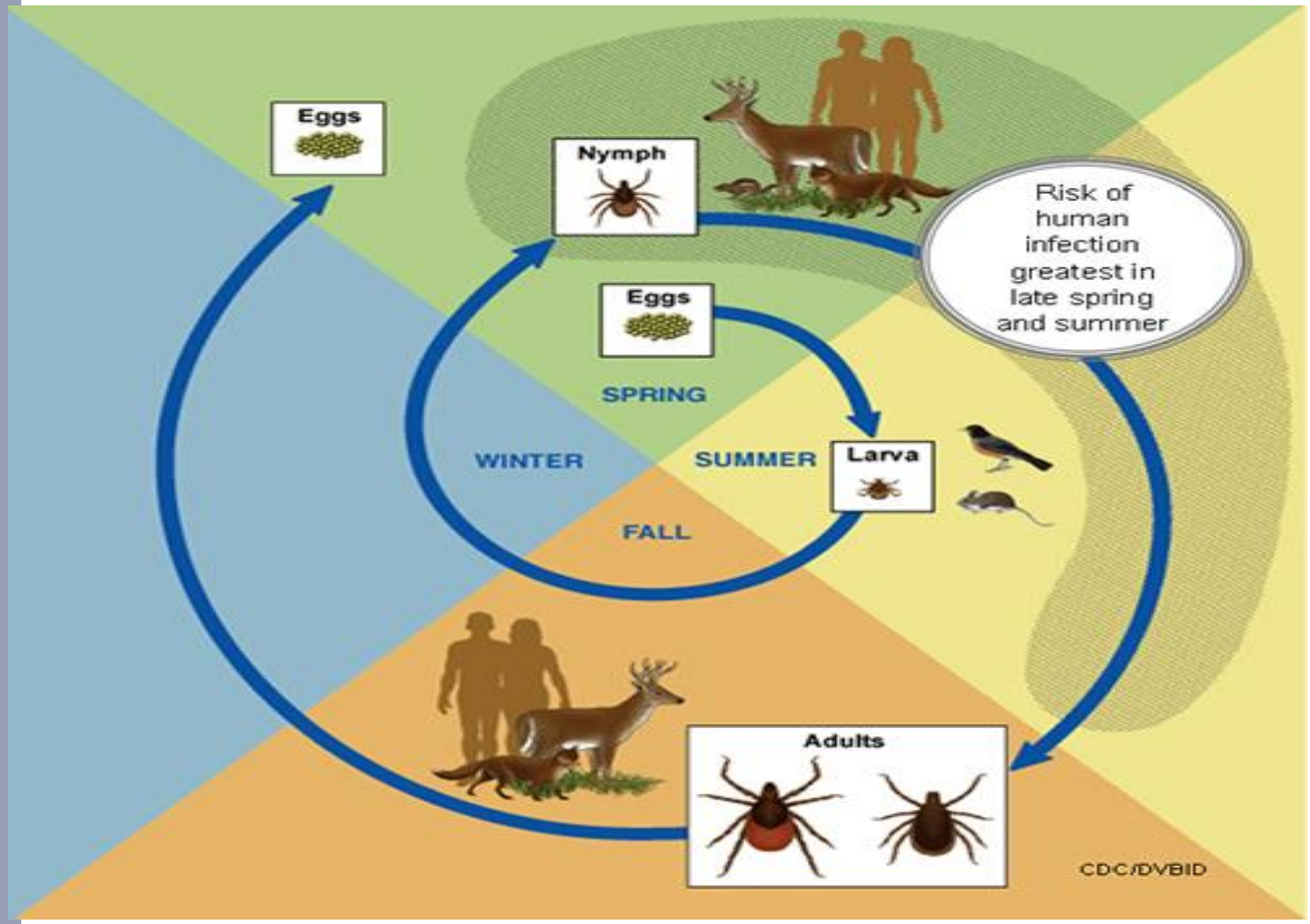
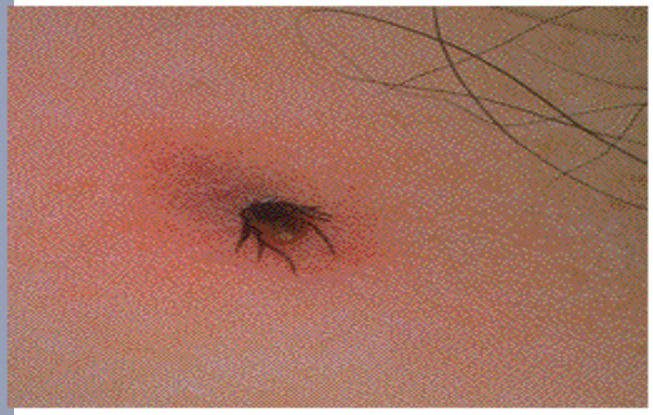
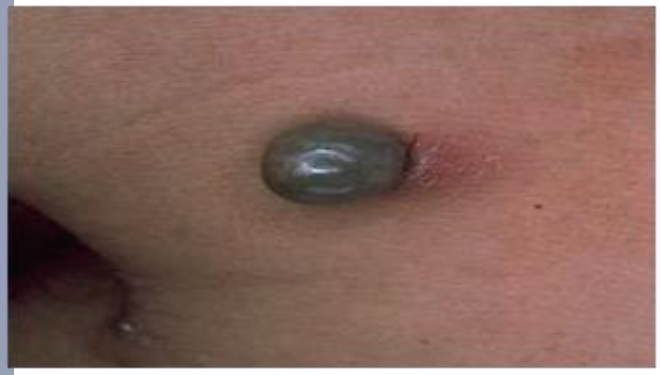
Tick vectors:

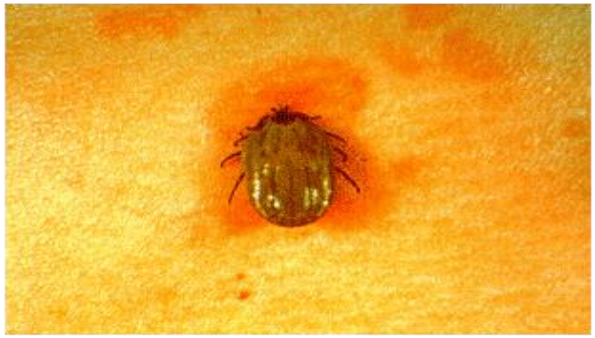
***B.burgdorferi* is transmitted to humans by ticks of the ixodes recinus complex**



Tick Bites







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 afzelli with acrodermatitis,…)**

Clinical stages of Lyme disease

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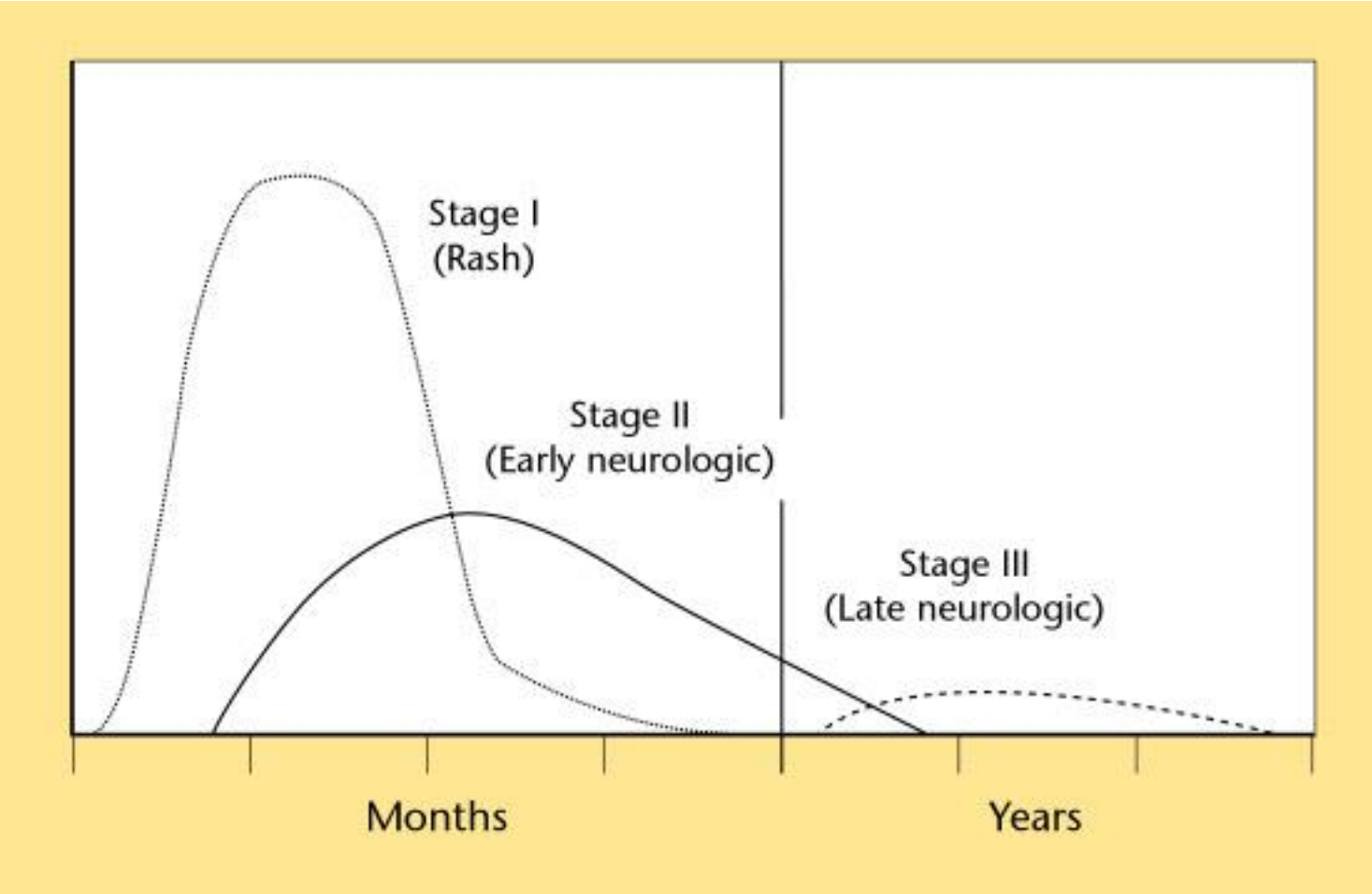
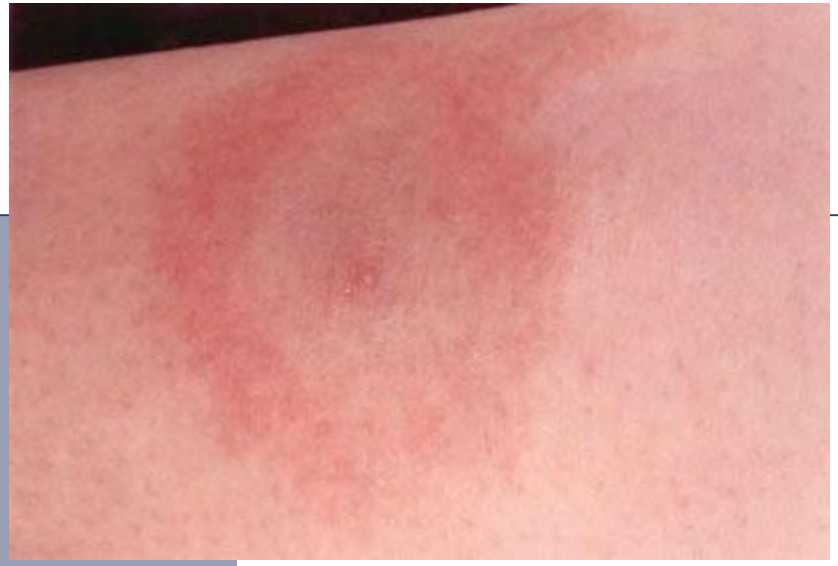
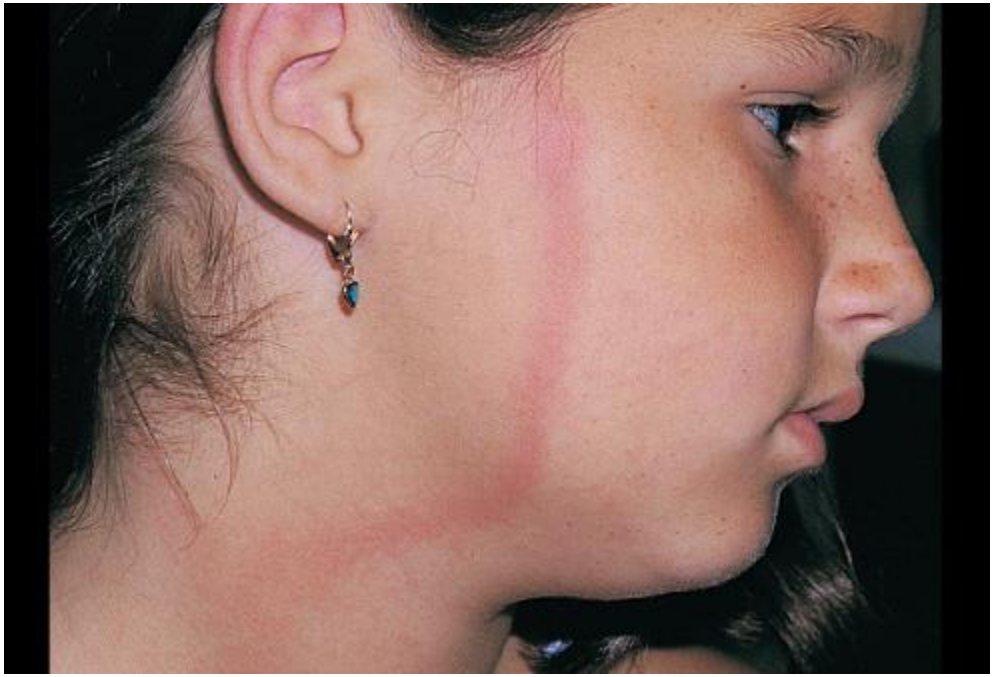


Clinical stages of Lyme disease

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 Borrrelia 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 2nd and 3rd 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 sympathic 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 symtoms, 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

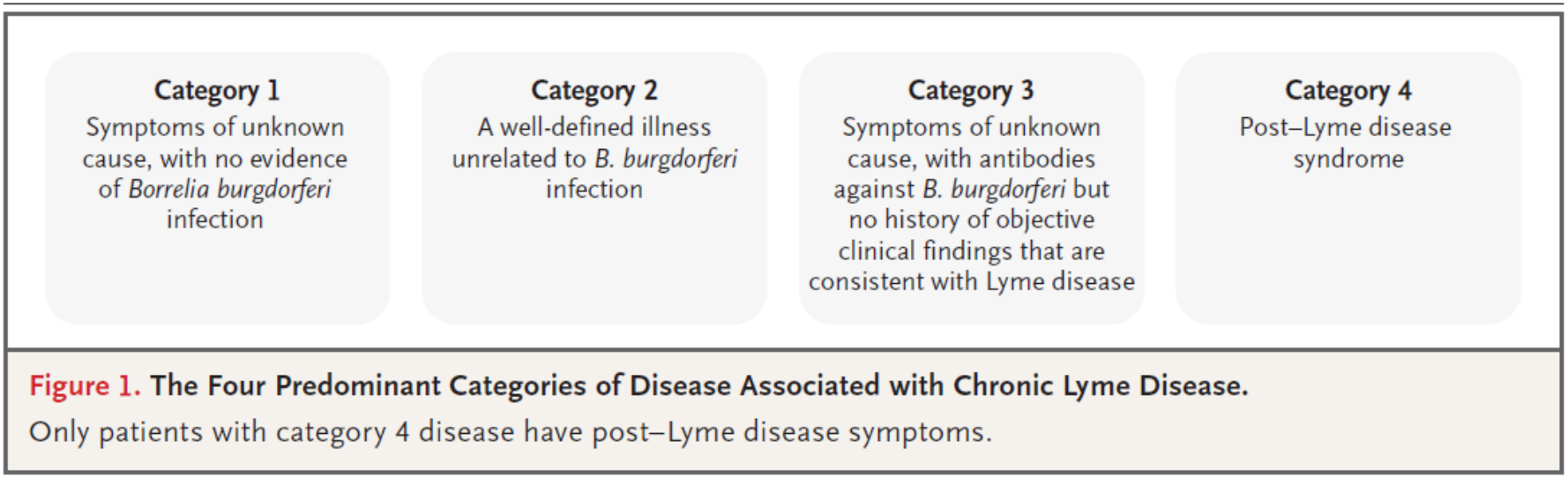


Figure 1. The Four Predominant Categories of Disease Associated with Chronic Lyme Disease.
Only patients with category 4 disease have post–Lyme disease symptoms.

Feder HM et al, N Engl J Med 2007;357:1422.

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

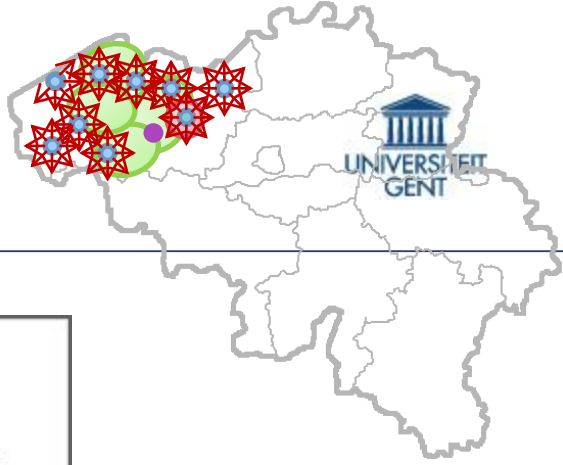
Signs and symptoms
Absence of concomitant objective clinical signs of either disease or inflammation and no progression to objective signs or development of inflammation[29,32]
Similar symptoms common in persons who have never had Lyme disease[24,25,30,31,48]
Laboratory tests
Persistence of symptoms 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]

Feder HM et al,
N Engl J Med 2007;357:1422.

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 sympoms + positive Borrelia burgdorferi IgG or IgM**
- **No baseline difference between groups**
- **Significant functional impact (low SF36)**

Berende et al. N Engl J Med 2016; 1209-1220



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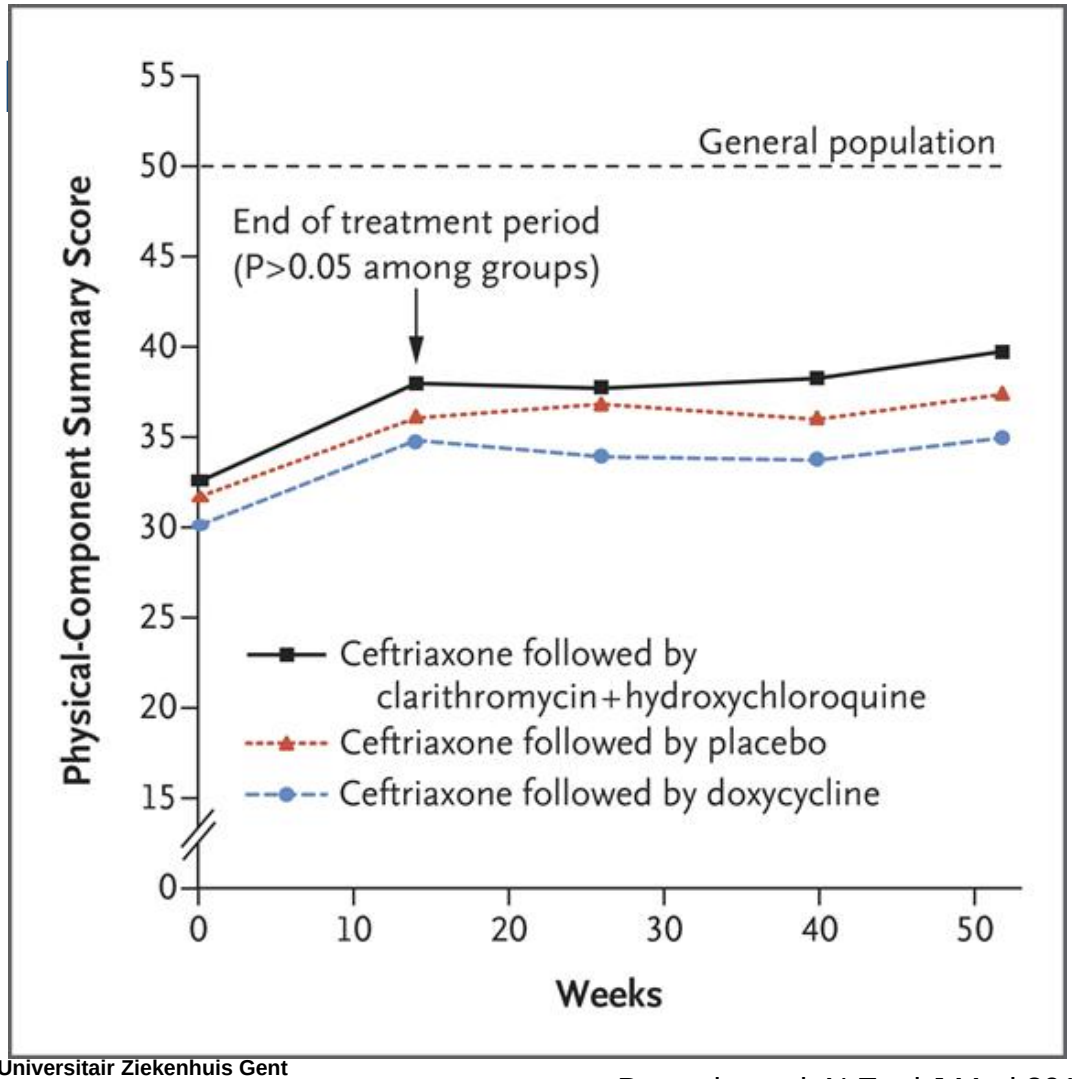

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PLEASE study

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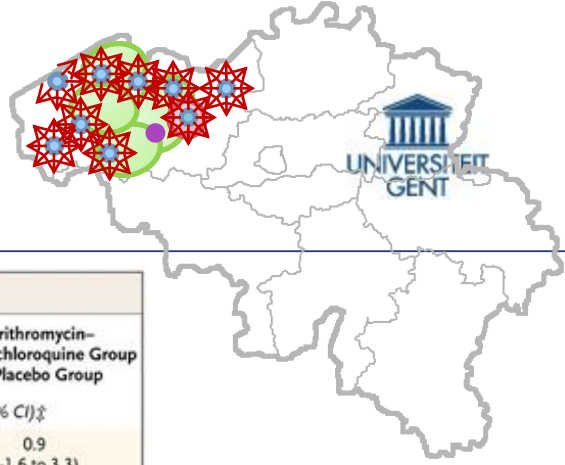

Table 2. Treatment Effect at the End of the Treatment Period in the Modified Intention-to-Treat Population.*

Outcome	Doxycycline Group (N=86)	Clarithromycin–Hydroxychloroquine Group (N=96)	Placebo Group (N=98)	P Value†	Doxycycline Group vs. Placebo Group	Clarithromycin–Hydroxychloroquine Group vs. Placebo Group
		score (95% CI)			*difference in score (95% CI)‡*	
Primary outcome: SF-36 physical-component summary§	35.0 (33.5 to 36.5)	35.6 (34.2 to 37.1)	34.8 (33.4 to 36.2)	0.69	0.2 (−2.4 to 2.8)	0.9 (−1.6 to 3.3)
Secondary outcomes						
RAND SF-36§						
Mental-component summary	40.2 (38.6 to 41.9)	40.5 (38.9 to 42.1)	40.1 (38.6 to 41.7)	0.94	0.1 (−2.7 to 2.9)	0.4 (−2.3 to 3.1)
Global-health composite	36.1 (34.5 to 37.8)	36.6 (35.1 to 38.1)	36.0 (34.5 to 37.5)	0.85	0.1 (−2.6 to 2.9)	0.6 (−2.1 to 3.2)
Physical-functioning scale	41.9 (40.5 to 43.3)	42.1 (40.8 to 43.4)	41.0 (39.7 to 42.3)	0.44	0.9 (−1.4 to 3.2)	1.1 (−1.1 to 3.4)
Role–physical scale	33.6 (31.6 to 35.6)	34.4 (32.5 to 36.3)	33.9 (32.0 to 35.8)	0.84	−0.3 (−3.7 to 3.1)	0.5 (−2.8 to 3.8)
Bodily pain scale	39.1 (37.5 to 40.7)	40.5 (39.0 to 41.9)	39.4 (37.9 to 40.9)	0.42	−0.3 (−2.9 to 2.4)	1.1 (−1.5 to 3.6)
General-health scale	37.1 (35.6 to 38.6)	38.4 (37.0 to 39.8)	37.5 (36.2 to 38.9)	0.41	−0.4 (−2.9 to 2.0)	0.9 (−1.5 to 3.3)
Mental-health scale	45.1 (43.8 to 46.4)	45.2 (43.9 to 46.4)	45.1 (43.9 to 46.4)	1.00	0.0 (−2.3 to 2.2)	0.0 (−2.1 to 2.2)
Role–emotional scale	44.7 (42.4 to 47.0)	41.4 (39.2 to 43.6)	42.6 (40.4 to 44.8)	0.11	2.1 (−1.7 to 6.0)	−1.2 (−5.0 to 2.6)
Social-functioning scale	36.3 (34.2 to 38.4)	38.5 (36.6 to 40.5)	37.5 (35.6 to 39.5)	0.32	−1.2 (−4.7 to 2.3)	1.0 (−2.4 to 4.4)
Vitality scale	42.5 (40.9 to 44.0)	42.4 (41.0 to 43.9)	41.9 (40.5 to 43.4)	0.85	0.5 (−2.0 to 3.1)	0.5 (−2.0 to 3.0)
Checklist Individual Strength¶						
Total score	88.7 (84.4 to 92.9)	87.1 (83.0 to 91.1)	88.4 (84.4 to 92.4)	0.84	0.3 (−6.9 to 7.4)	−1.3 (−8.3 to 5.6)
Fatigue-severity scale	39.4 (37.3 to 41.5)	38.6 (36.6 to 40.5)	38.3 (36.3 to 40.2)	0.73	1.1 (−2.4 to 4.6)	0.3 (−3.1 to 3.7)

* 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, 26 to 56; bodily pain 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.

Berende et al. N Engl J Med 2016; 1209-1220

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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BAPCOC
Belgian Antibiotic Policy Coordination Committee

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