Lyme borreliosis
Diagnosis and Treatment



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Diclosures

Consultant to Baxter regarding Lyme vaccine
(function ended in 2013)

Member of the Steering committee of ESCMID Study Group on Lyme Borreliosis/ESGBOR

- Early localized illness
  - Erythema migrans
  - Borrelial lymphocytoma
- Early disseminated illness
  - Multiple erythema migrans lesions
  - Neurologic involvement
  - Heart involvement
  - Joint involvement
- Late illness
  - Arthritis
  - Nervous system involvement
  - Acrodermatitis chronica atrophicans

→ Diagnosis

and

Treatment

Diagnosis of Lyme borreliosis

- Recognition of (individual) clinical manifestation

and

- Demonstration of borrelial etiology of the manifestation

(serum antibodies to *Borrelia*)

Clinical diagnosis

Typical skin manifestations



Erythema migrans

- Borrelial lymphocytoma
- Acrodermatitis chronica atrophicans

Meningoradiculoneuritis (Bannwarth's syndrome)

Demonstration of borrelial infection























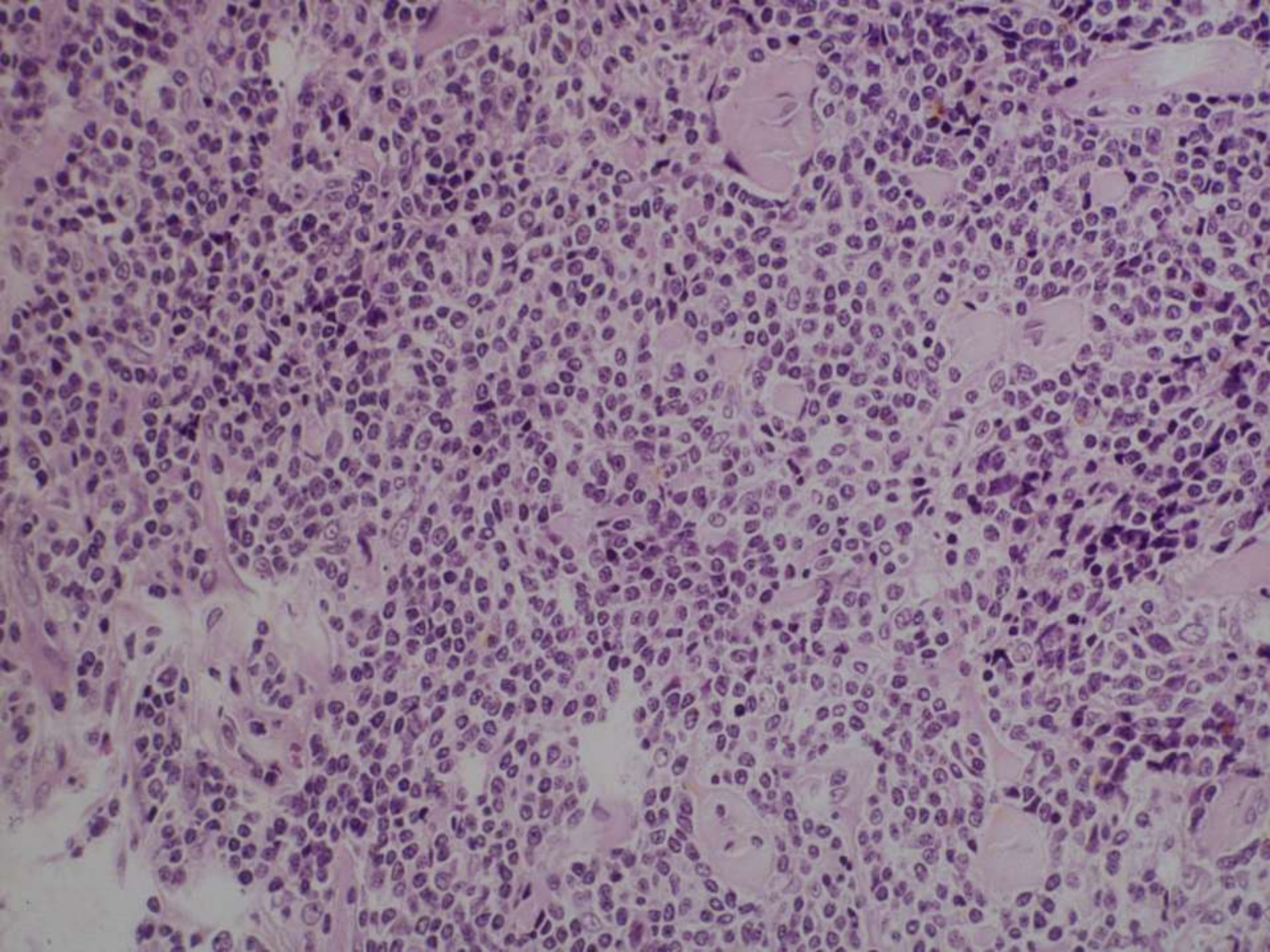

Stanek G, Fingerle F, Hunfeld KP, Jaulhac B, et al. Lyme borreliosis: Clinical case definitions for diagnosis and management in Europe. *Clin Microbiol Infect* 2011; 17: 69–79.

ERYTHEMA MIGRANS

Clinical case definition	Laboratory evidence: essential	Laboratory/**clinical evidence: supporting**
Expanding red or bluish-red **patch ≥5 cm in diameter* central clearing + or -** Advancing edge typically distinct, often intensely coloured, not markedly elevated.	None	Detection of Bb s.l. by culture and/or PCR from skin biopsy.

*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.















Stanek G, Fingerle F, Hunfeld KP, Jaulhac B, et al. Lyme borreliosis: Clinical case definitions for diagnosis and management in Europe. *Clin Microbiol Infect* 2011; 17: 69–79.

BORRELIAL LYMPHOCYTOMA

Clinical case definition	Laboratory evidence: essential	Laboratory/**clinical evidence: supporting**
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. Histology in unclear cases.	Histology. Detection of Bb s.l. by culture/PCR from skin biopsy. Recent or concomitant EM.













Stanek G, Fingerle F, Hunfeld KP, Jaulhac B, et al. Lyme borreliosis: Clinical case definitions for diagnosis and management in Europe. *Clin Microbiol Infect* 2011; 17: 69–79.

ACRODERMATITIS CHRONICA ATROPHICANS

Clinical case definition	Laboratory evidence: essential	Laboratory/**clinical evidence: supporting**
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 Bb s.l. by culture/PCR from skin biopsy.

Clinical diagnosis

Typical skin manifestations



Erythema migrans

- Borrelial lymphocytoma
- Acrodermatitis chronica atrophicans

Meningoradiculoneuritis (Bannwarth's syndrome)

Clinical diagnosis

Typical skin manifestations



Erythema migrans

- Borrelial lymphocytoma
- Acrodermatitis chronica atrophicans

Meningoradiculoneuritis (Bannwarth's syndrome)

Signs of involvement of: nervous system
joints
hearth
eyes

Approaches:

- search for the presence of "typical signs" of LB
- demonstration of borrelial infection (serum antibodies)
- demonstration of borrelial infection of the involved organ
- search for and exclusion of other reasons (explanations)

Clinical diagnosis

Typical skin manifestations



- **Erythema migrans**
- Borrelial lymphocytoma
- Acrodermatitis chronica atrophicans

Meningoradiculoneuritis (Bannwarth´s syndrome)

Signs of involvement of: nervous system
joints
hearth
eyes

Approaches:

search for the presence of "typical signs" of LB
demonstration of borrelial infection (serum antibodies)
demonstration of borrelial infection of the involved organ
search for and exclusion of other reasons (explanations)

Clinical diagnosis

Typical skin manifestations



Erythema migrans

- Borrelial lymphocytoma
- Acrodermatitis chronica atrophicans

Meningoradiculoneuritis (Bannwarth's syndrome)

Symptoms (without objective signs):

Approaches:

- search for the presence of (typical) signs of LB
- demonstration of borrelial infection of the involved organ
- demonstration of borrelial infection (serum antibodies)
- search for other reasons (explanations)
- CAUTION

Diagnosis – general remarks

Importance of proper diagnosis

A reliable diagnosis constitutes the basis for rational treatment

Careful history and physical examination



"Those bullet holes are something new, aren't they?"















Diagnosis – general remarks

Importance of proper diagnosis

A reliable diagnosis constitutes the basis for rational treatment

Difficulties with diagnosis:

⟶ objective

subjective:

- limited knowledge
- other reasons

Diagnosis – general remarks

Importance of proper diagnosis

A reliable diagnosis constitutes the basis for rational treatment

Difficulties with diagnosis: objective

⟶ subjective:

- limited knowledge
- other reasons





Diagnosis – general remarks

Importance of proper diagnosis

A reliable diagnosis constitutes the basis for rational treatment

Difficulties with diagnosis:

objective

subjective:

- limited knowledge
- other reasons

→ Difficulties with patients who probably do not have LB but are convinced that they have it

Relationship patient : doctor ...



"I hope you are not going to be like the twenty incompetent doctors who couldn't find anything wrong with me. I tell you, I have Lyme!!!"

Approaches to laboratory diagnostics



“I’ll want to run a few tests on you, just to cover my ass.”

Diagnosis – general remarks
Chronic LB, Sequelae after LB

Chronic Lyme borreliosis:

Definition: objective manifestations of late LB with the duration of ≥6 months

How it is diagnosed?

- Objective clinical manifestation +
- Demonstration of borrelia infection (of the organ involved) +
- Exclusion of other causes

How frequent it is?

Frequency of main clinical manifestations of LB

Department of Infectious Diseases,
UMC Ljubljana, Slovenia

2005

Frequency of main clinical manifestations of LB

Manifestation	Adults	Children	p
EM 82%	621 (83.4%)	218 (79.3%)	0.1549
SEM	585 (78.5%)	136 (49.5%)	0.0000
MEM	36 (4.8%)	82 (29.8%)	0.0000
BL	4 (0.5%)	4 (1.5%)	0.2220
LNB 9%	48 (6.4%)	40 (14.5%)	0.0001
LC	2 (0.3%)	0	
LA 3%	21 (2.8%)	13 (4.7%)	0.1901
ACA 5%	49 (6.6%)	0	0.0000
∑	745	275	1020

Frequency of main clinical manifestations of LB

Manifestation	Adults	Children	p
EM	621 (83.4%)	218 (79.3%)	0.1549
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LNB	48 (6.4%)	40 (14.5%)	**0.0001**
LC	2 (0.3%)	0	
LA	21 (2.8%)	13 (4.7%)	0.1901
ACA	49 (6.6%)	0	**0.0000**
∑	745	275	1020

Frequency of main **late** clinical manifestations of LB

Manifestation	Adults	Children	Late
EM	621 (83.4%)	218 (79.3%)	**0**
BL	4 (0.5%)	4 (1.5%)	**0**
LNB	48 (6.4%) **3**	40 (14.5%) **0**	**3**
LC	2 (0.3%)	0	**0**
LA	21 (2.8%) **2**	13 (4.7%) **2**	**4**
ACA	49 (6.6%) **49**	0	**49**
∑	**54**/745 **(7.2%)**	**2**/275 **(0.7%)**	**56**/1020 **(5.5%)**

Diagnosis

and

→ Treatment

Clinical Infectious Diseases® 2015;60(12):1776–82

Unorthodox Alternative Therapies Marketed to Treat Lyme Disease

Paul M. Lantos,[1] Eugene D. Shapiro,[2] Paul G. Auwaerter,[3] Phillip J. Baker,[4] John J. Halperin,[5,6] Edward McSweegan,[7] and Gary P. Wormser[8]

[1]Divisions of Pediatric Infectious Diseases and General Internal Medicine, Duke University Medical Center, Durham, North Carolina; [2]Departments of Pediatrics, Epidemiology of Microbial Diseases and Investigative Medicine, Yale University Schools of Medicine and of Public Health and Graduate School of Arts and Sciences, New Haven, Connecticut; [3]Division of Infectious Diseases, Fisher Center for Environmental Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, Maryland; [4]American Lyme Disease Foundation, Lyme, Connecticut; [5]Department of Neurosciences, Overlook Medical Center, Atlantic Health System, Summit, New Jersey; [6]Departments of Neurology and Medicine, Icahn School of Medicine at Mount Sinai, New York, New York; [7]Global Virus Network, Baltimore, Maryland; and [8]Division of Infectious Diseases, New York Medical College, Valhalla, New York

(See the Editorial Commentary by Steere and Arvikar on pages 1783–5.)

Background. Some patients with medically unexplained symptoms or alternative medical diagnoses suspect that they chronically suffer from the tick-borne infection Lyme disease. These patients are commonly targeted by providers of alternative therapies. This study was designed to identify and characterize the range of unorthodox alternative therapies advertised to patients with a diagnosis of Lyme disease.

Methods. Internet searches using the Google search engine were performed to identify the websites of clinics and services that marketed nonantimicrobial therapies for Lyme disease. We subsequently used the PubMed search

Table 1. Examples of Alternative Medical Therapies Marketed to Patients for the Treatment of Lyme Disease

Categories of Therapy	Examples
Oxygen	Hyperbaric oxygen Hydrogen peroxide Ozone
Energy and radiation	Ultraviolet light Photon therapy "Cold" lasers Saunas and steam rooms "Rife" therapy (electromagnetic frequency treatments) Magnets
Metal/chelation	Mercury chelation and removal Dimercaptosuccinic acid (DMSA) 2,3-Dimercapto-1-propanesulfonic acid (DMPS) Alpha lipoic acid (ALA) Ethylene diamine tetraacetic acid (EDTA) Removal of dental amalgam Colloidal silver Bismuth
Nutritional	Vitamins C and B12

	Bismuth
Nutritional supplements	Vitamins C and B12 Herbs Garlic, cilantro, Chlorella, Sarsaparilla, Andrographis, Turmeric, Olive leaf, Cat's claw Burnt mugwort (moxibustion) Glutathione Fish oil Magnesium Salt
Biological and pharmacologic	Urotherapy (urine ingestion) Enemas Bee venom Hormonal therapy Dihidroepiandrostenedione, Pregnenolone, Cortisone, Hydrocortisone Synthetic thyroid hormone Lithium orotate Olmesartan Cholestyramine Naltrexone Sodium chlorite (bleach) Intravenous immune globulin (IVIG) Apheresis Stem cell transplantation

Diagnosis
and
→ AntibioticTreatment

General remarks

- Treatment with antibiotics is reasonable for all clinical manifestations of LB. It is most effective early in the course of the disease.
- The purpose of treating a patient with LB is

  to heal existing manifestation(s) and

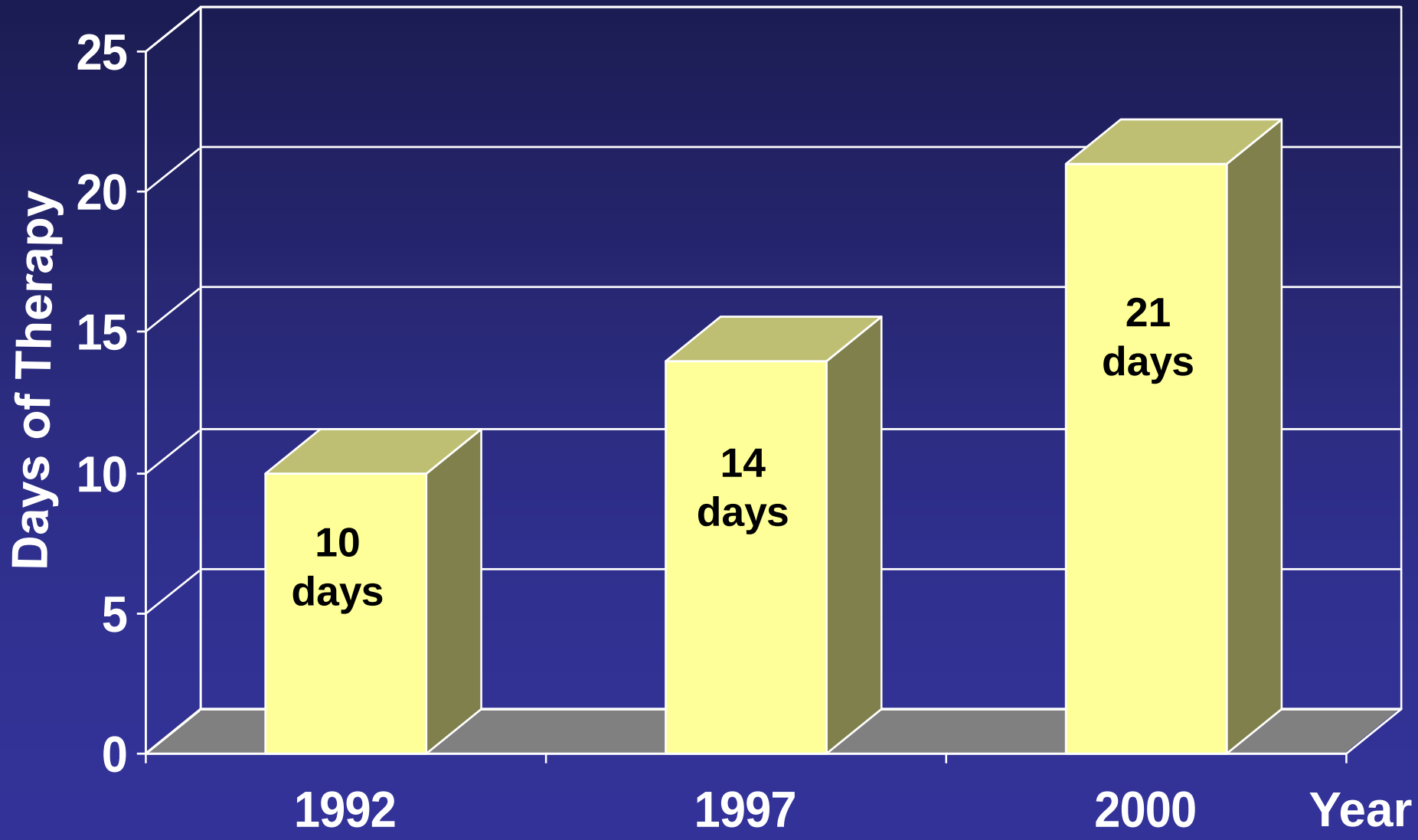
  to prevent progression of the illness.
- Only antibiotics with *in vitro* activity against *Borreliae* that were found to be effective in clinical studies should be utilized for therapy of LB.

General remarks

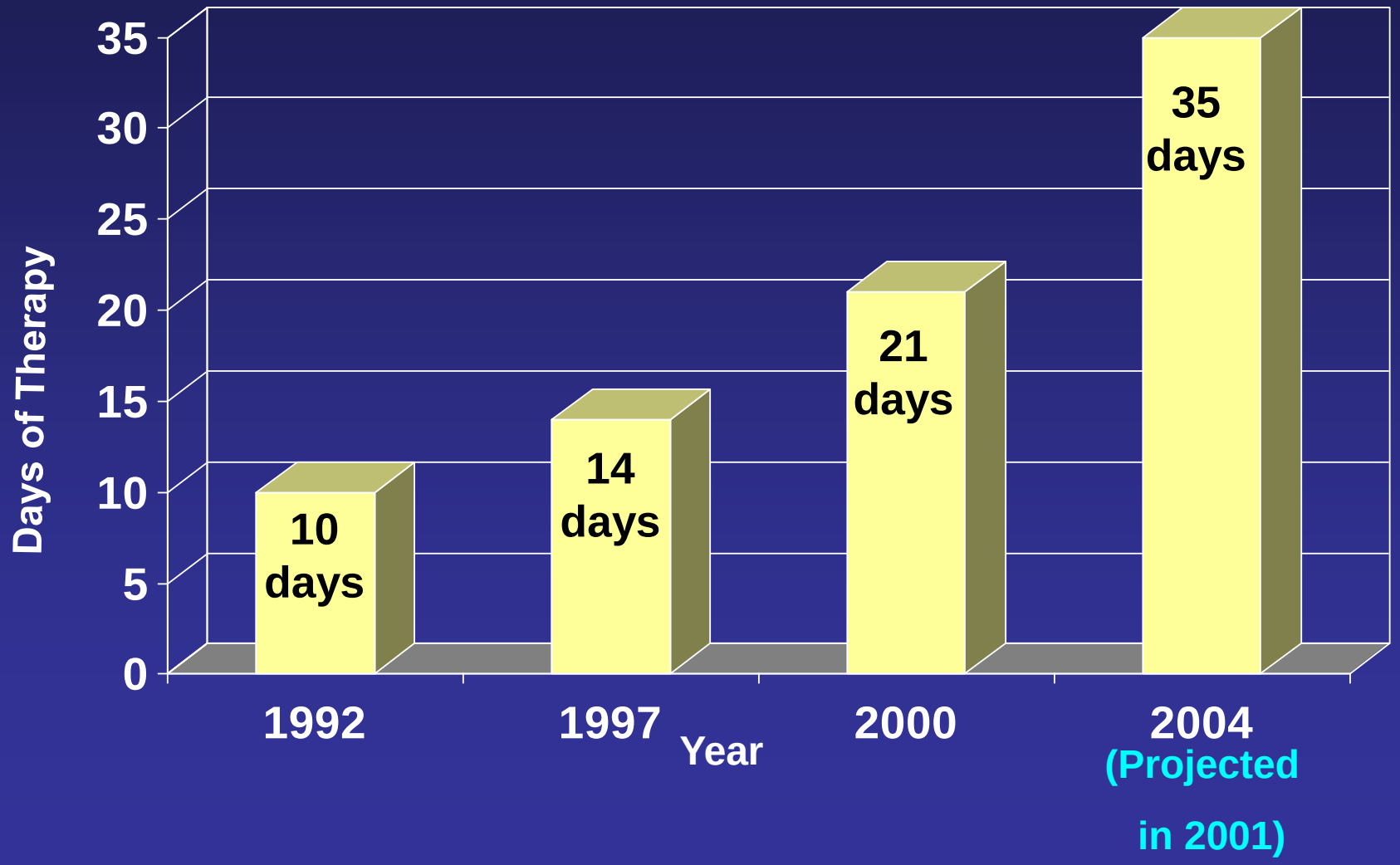
Prerequisites for a successful treatment of LB are:

- Effective antibiotic with a favorable pharmacokynetic properties
- Optimal dosing
- Appropriate duration of treatment

Minimum Duration Antibiotic Therapy for Treatment of Patients with EM over 9 Year Time Span



Minimum Duration Antibiotic Therapy for Treatment of Patients with EM



„Recent“ studies comparing the efficacy of longer and shorter antibiotic treatment

- Wormser GP et al. Duration of antibiotic therapy for early Lyme disease. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 2003; 138: 679-704.
- Dattwyler RJ et al. A comparison of two treatment regimens of ceftriaxone in late Lyme disease. Wien Klin Wochenschr 2005; 117: 393-7.
- Oksi J et al. Duration of antibiotic treatment in disseminated Lyme borreliosis: a double-blind, randomized, placebo-controlled, multicenter clinical study. Eur J Clin Microbiol Infect Dis. 2007;26:571-81
- Cerar D, et al. Subjective Symptoms after Treatment of Early Lyme Disease. Am J Med 2010; 123: 79-86

General remarks

Advantages of shorter courses of antibiotic treatment

- Safer
- Less costly
- More convenient for patient
- Less ecological effects (resistance)

General remarks

Reasons for antibiotic treatment failure

Persistence of *Borreliae* in tissues

Unreparable tissue lesion

Induction of autoimmune mechanisms

Wrong diagnosis

" Treatment of serological tests "
(= treatment of antibody titres, …)

Difficult decissions



„It’s got to come out, of course, but that doesn’t address the deeper problem”

General remarks

Treatment recommendations for LB are based on: - treatment studies and on
- clinical experience

No randomized prospective blinded and placebo controlled trials

Antibiotic treatment of Lyme borreliosis

Stanek G, Wormser GP, Gray JS, Strle F. Lyme borreliosis. Lancet 2012; 379: 461-73.

ERYTHEMA MIGRANS, LYMPHOCYTOMA

ANTIBIOTIC	Mode	Duration (days)	Contraindications
DOXYCYCLINE	o.	14 (10-14)	children, pregnancy, lactation, allergy
AMOXICILLIN	o.	14	allergy
PENICILLIN V	o.	14	allergy
CEFUROXIME	o.	14	allergy
AZITHROMYCIN	o.	5	allergy
ERYTHROMYCIN	o.	14	allergy
CEFTRIAXONE	i.v.	14	allergy
PENICILLIN G	i.v.	14	allergy

ACRODERMATITIS CHRONICA ATROPHICANS

ANTIBIOTIC	Mode	Duration (days)	Contraindications
DOXYCYCLINE	o.	21-28	children, pregnancy, lactation, allergy
AMOXICILLIN	o.	21-28	allergy
PENICILLIN V	o.	21-28	allergy
CEFUROXIME	o.	21-28	allergy
CEFTRIAXONE	i.v.	21-28	allergy
PENICILLIN G	i.v.	21-28	allergy

Early LNB, Hearth involvement

ANTIBIOTIC	Dose	Mode	Duration (days)	Contra-indications
CEFTRIAXONE	2g od	i.v.	14 (10-21)	allergy
PENICILLIN G	20MU	i.v.	14 (10-21)	allergy
CEFOTAXIME	2g tid	i.v.	14 (10-21)	allergy
DOXYCYCLINE	100mg bid	o .	14 (10-30)	children, pregnancy, lactation, allergy

Recommendations for antibiotic treatment of patients with late LNB

ANTIBIOTIC	Dose	Mode	Duration (weeks)	Contra-indications
CNS involvement				
CEFTRIAXONE	2g od	i.v.	2-4	allergy
PENICILLIN G	20MU	i.v.	2-4	allergy
CEFOTAXIME	2g tid	i.v.	2-4	allergy
ACA associated neuropathy				
Treated as ACA withouth neuropathy				

ARTHRITIS (initial treatment)

ANTIBIOTIC	Mode	Duration (days)	Contraindications
DOXYCYCLINE	o.	28	children, pregnancy, lactation, allergy
AMOXICILLIN	o.	28	allergy
PENICILLIN V	o.	28	allergy
CEFUROXIME	o.	28	allergy
CEFTRIAXONE	i.v.	14-28	allergy
PENICILLIN G	i.v.	14-28	allergy

RECURRENT ARTHRITIS
(after one course of oral treatment)

ANTIBIOTIC	Mode	Duration (days)	Contraindications
DOXYCYCLINE	o.	28	children, pregnancy, lactation, allergy
AMOXICILLIN	o.	28	allergy
PENICILLIN V	o.	28	allergy
CEFUROXIME	o.	28	allergy
CEFTRIAXONE	i.v.	14-28	allergy
PENICILLIN G	i.v.	14-28	allergy

Sequellae of Lyme borreliosis

Definition: (new or increased) signs/symptoms (≥6 months) after treatment with currently recommended regimens

General remarks
Chronic LB, Sequellae of LB

Sequellae of Lyme borreliosis:

→ **Objective sequellae** (signs)

Subjective sequellae (symptoms)

General remarks
Chronic LB, Sequellae of LB

Sequellae of Lyme borreliosis:

Objective sequellae

→ **Subjective sequellae (symptoms)**

Post Lyme disease syndrome

(>6 m; severe)

General remarks
Chronic LB, Sequellae of LB

Subjective sequellae of Lyme borreliosis

The appearance seems to correlate with:

disseminated disease,

a greater severity of illness at presentation,

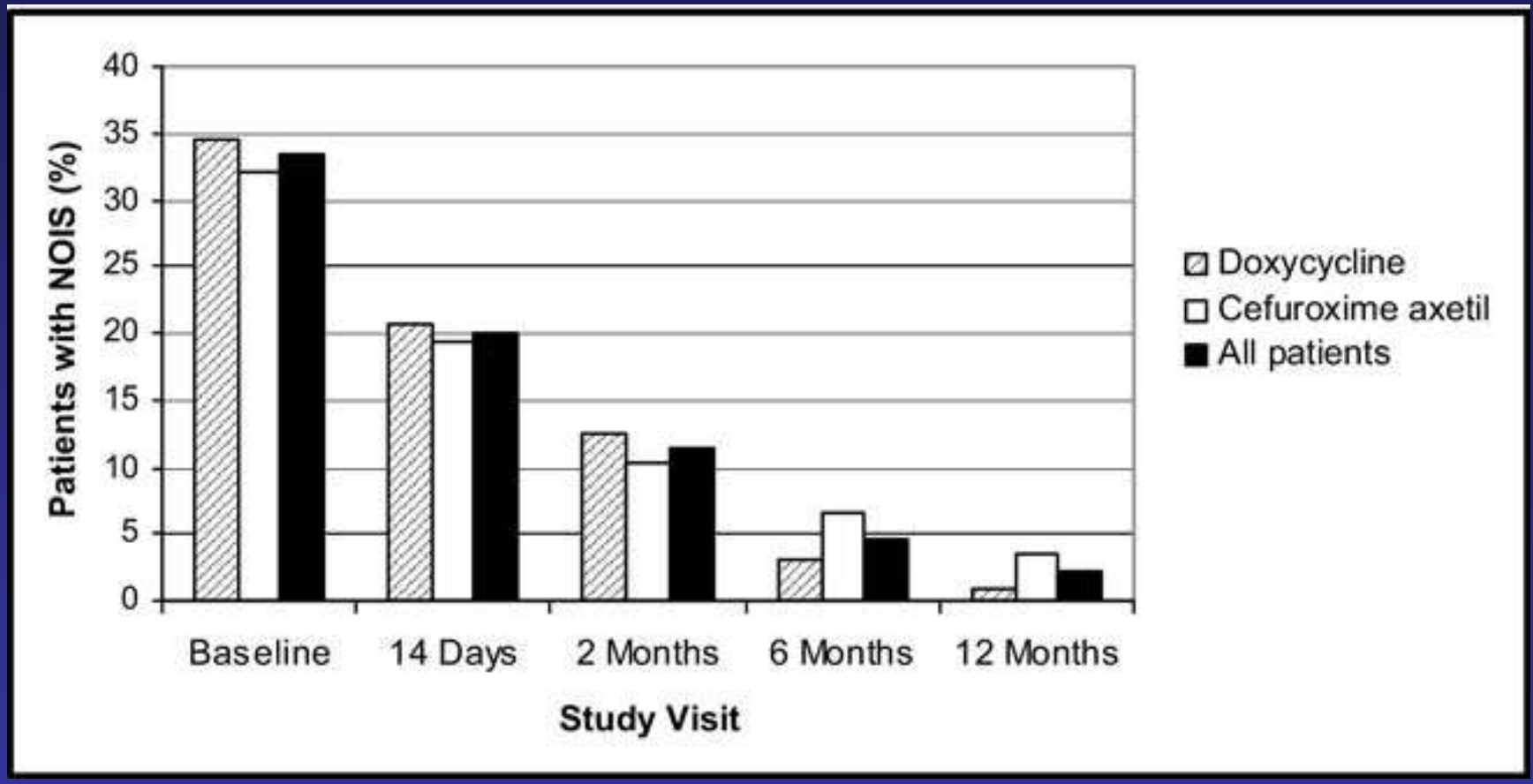
delayed antibiotic treatment,

but not with:

duration of the initial antibiotic treatment.

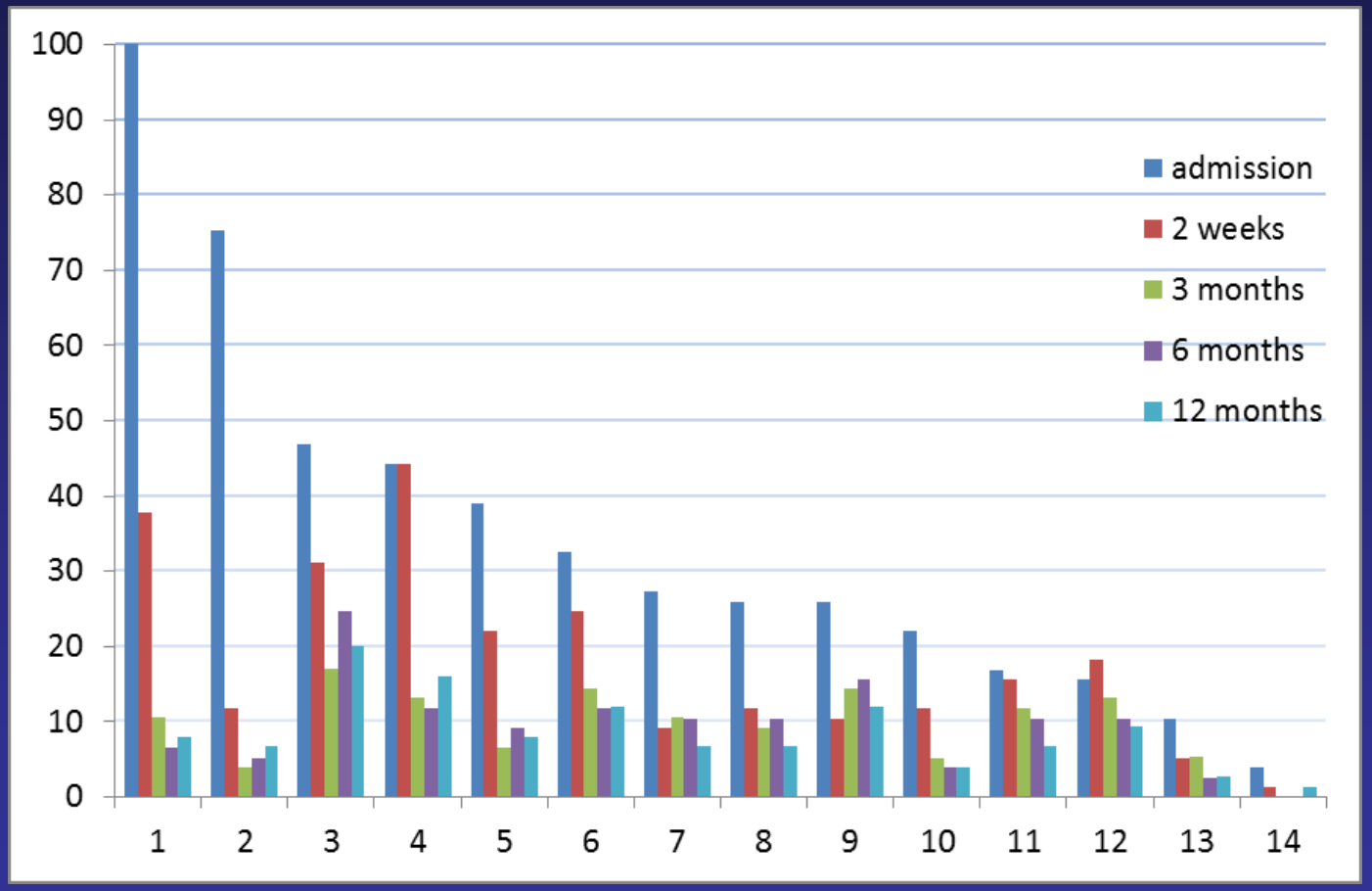
Appear to be less likely in children

Subjective sequellae of LB



Cerar D, et al. Subjective Symptoms after Treatment of Early Lyme Disease. Am J Med 2010; 123: 79-86

The frequency of individual symptoms at admission and at follow-up visits in 77 adult patients with Bannwarth's syndrome, treated with ceftriaxone (2 g od iv for 14 days).



1- radicular pain; 2- sleep disturbances; 3- headache; 4- fatigue; 5- malaise; 6- paresthesias; 7- back pain; 8- mialgias; 9- arthralgias; 10- neck pain; 11- concentraction disorders; 12- memory disorders; 13- nausea; 14- vomiting.

TREATMENT of an ASYMPTOMATIC PERSON after a TICK BITE

???

WAIT and WATCH

TREATMENT of a PERSON with a SMALL REDNESS at the SITE of a TICK BITE

that develops within the

FIRST 24 HOURS after the BITE

???

WAIT and WATCH

Treatment of ASYMPTOMATIC PERSONS with POSITIVE BORRELIAL SERUM ANTIBODY TITRES

???

WAIT and WATCH

A PATIENT with MYALGIA, ARTHRALGIA, HEADACHE, FATIGUE

WITHOUT SIGNS INDICATIVE of LB

???

APPROACH:

DO NOT PERFORM

SEROLOGICAL TESTING

TREATMENT of a PATIENT with MYALGIA, ARTHRALGIA, HEADACHE, FATIGUE … and POSITIVE SERUM BORRELIAL ANTIBODY TITRES

???

APPROACH:

RE-CHECK the DIAGNOSIS

SEARCH for an ALTERNATIVE EXPLANATION

???ANTIBIOTICS???

TREATMENT of a PATIENT with MYALGIA, ARTHRALGIA, HEADACHE, FATIGUE … and POSITIVE SERUM BORRELIAL ANTIBODY TITRES

???

OTHER EXPLANATION (DIAGNOSIS) **FOUND**

NO ANTIBIOTICS

TREATMENT of a PATIENT with MYALGIA, ARTHRALGIA, HEADACHE, FATIGUE … and POSITIVE SERUM BORRELIAL ANTIBODY TITRES

???

OTHER EXPLANATION (DIAGNOSIS)
NOT FOUND

?ANTIBIOTICS?

TREATMENT of a PATIENT with MYALGIA, ARTHRALGIA, HEADACHE, FATIGUE … and POSITIVE SERUM BORRELIAL ANTIBODY TITRES

???

APPROACH:

- Discuss the problem of **theoretical possibility of Lyme borreliosis** with the patient (negotiate)
- Agree with eventual **"treatment trial"**
- Do **not** offer **repeated treatment** with antibiotics

Conclusions

LB still presents

- a substantial medical burden

and

- challenge for further work and research.

Conclusions

There are several unresolved issues concerning pathogenesis, diagnosis, treatment and prevention of LB with consequential practical problems in the management of patients.

However, there are also several "fictitious" problems, which seem to be increasing much faster than the real problems are resolving.



Objective sequelae of Lyme borrelisis

Manifestation	Sequelae	Persistence of borreliae	Irreversible damage	Autoimmune mechanisms
EM	-	- (?+ 0-3%)	-	-
BL	-	- (no studies)	-	-
LNB	+	- (limited data)	+	- (limited data)
LA	+	-/+ (limited data)	+ (ACA)	+
ACA	+	- (limited data)	+	- (limited data)