Treatment regimens for Lyme neuroborreliosis within the sway of antibiotic maximalism

W. Kristoferitsch

Karl-Landsteiner-Institute for
Neuroimmunological and Neurodegenerative Disorders
SMZ-Ost-Donauspital, Vienna, Austria

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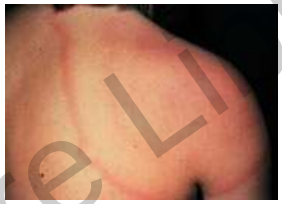
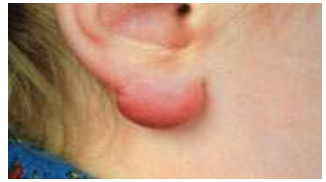
Lyme borreliosis (LB): clinical manifestations

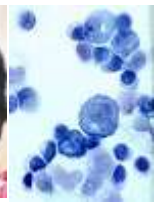
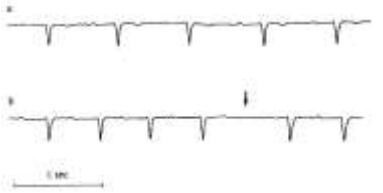
Early manifestations

Stage 1 (local)
- Erythema migrans

Stage 2 (early dissemination)
- Multilocular erythema migrans
- Lymphadenosis benigna cutis
- Meningoradiculoneuritis Bannwarth (adults)
- Myelitis, encephalitis, vasculitis (rare)
- Facial palsy and Meningitis (children)
- Carditis

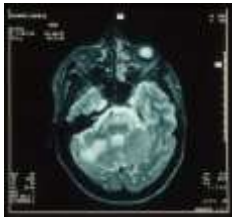
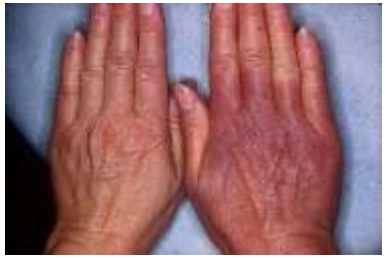
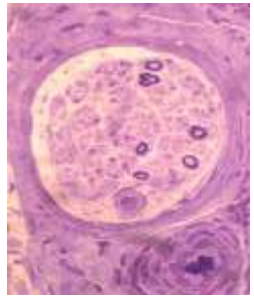




Late and chronic manifestations

Stage 3
- Chronic arthritis
- Acrodermatitis chronica atrophicans (ACA)
- ACA-associated chronic neuropathy
- Chronic aseptic meningitis
- Chronic progressing encephalomyelitis

Lyme neuroborreliosis (LNB): manifestations and frequency of occurrence

Stage	*Clinical features*	*%**
Infection of the nervous system unanimously accepted	Meningoradiculoneuritis } Bannwarth syndrome	61,0
	Radicular pain syndrome only } Bannwarth syndrome	24,6
	Meningoradiculomyelitis } Bannwarth syndrome	3,7
	Subacute meningitis [In children: meningitis / facial palsy without radicular pain syndrome]	4,8
Antibiotic Tx for 2-4 weeks highly effective	Chronic meningitis	1,6
	Chronic encephalitis / encephalomyelitis / vasculitis	4,3
	ACA associated neuropathy	-
Ongoing controversy on pathomechanism, definition and existence	„Lyme encephalopathy“	no data from Europe
	„Post Lyme disease syndrome“ (PLDS)	
	„Chronic Lyme disease“ / „Chronic Lyme“	

Chronic LNB, Lyme encephalopathy, PLDS and „Chronic Lyme“

	Syndrome	Signs / symptoms	Definition	Response to antibiotic Tx
Europe	Chronic or late LNB	Objective signs and symptoms for > 6 mths	Demonstration of ongoing CNS-infection	yes
USA	Lyme encephalopathy	Cognitive impairment	Objective evidence of ongoing LB without direct CNS involvement #	yes
	Post Lyme disease syndrome (IDSA)	Subjective symptoms*	Sx > 6 m after standard-Tx of LB, active infection not demonstrable	no
USA	„Chronic Lyme disease“; “Chronic Lyme“ (ILADS)§	Frequently subjective symptoms only*	Late symptoms hypothe-sized due to infection; regardless of previousTx	yes (ILADS)

imprecisely defined, overlap

initially considered as mild CNS infection or as „toxic, metabolic“ in origin.

*such as fatigue, cognitive impairment, headache, arthralgia, myalgia.

§ ill-defined synonym for chronic infection. ILADS: International Lyme and Associated Disease Society founded in 1999 by doctors who aggressively treated Lyme disease

IDSA: Infectious Disease Society of America

Chronic LNB, Lyme encephalopathy, PLDS, „Chronic Lyme“: frequency of occurrence

Europe

Chronic LNB: 5,9% of all cases with LNB *(Hansen and Lebech 1992).*

USA

Ten panel members of the IDSA 2006 Guidelines have diagnosed only one patient with late encephalomyelitis and only 7 patients with Lyme disease associated encephalopathy over the past 5 years *(Clin Infect Dis 2006;43:1089-1134).*

Of 5746 patients screened over 2,6-4,2 years, only 221 (3,8%) could be randomized for Tx-trials of PLDS *(Kaplan et al 2003; Krupp et al 2003, Fallon et al 2000).*

A former president of ILADS has treated >12.000 “Chronic Lyme Disease” patients in the last 20 years *[http://www.psychologytoday.com].*

Treatment of LB in Europe

http://www.eucalb.com

Drug	Route	Dosage*	Duration
Erythema migrans and borrelial lymphocytoma**			
Doxycyclin[1]	Oral	2x100 mg	14 (10-21) days
Amoxicillin	Oral	3x500-1000 mg	14 (10-21) days
Cefuroxim-Axetil	Oral	2x500 mg	14 (10-21) days
Penicillin V	Oral	3x1-1,5 Mio U	14 (10-21) days
Azithromyzin[2]	Oral	2x500 mg 1x500 mg	First day Next 4 days
Neuroborreliosis* **			
Ceftriaxone[3]	iv	2 g	14 (10-30) days
Penicillin G	iv	4x5 Mio U	14 (10-30) days
Doxycycline[1]	Oral	2x100 mg	14 (10-30) days
Arthritis, Karditis, Acrodermatitis chronica atrophicans			
Doxycyclin[1]	Oral	2x100 mg	14 (10-30) days
Amoxicillin	Oral	3x500-1000 mg	14 (10-30) days
Ceftriaxone[3]	iv	2 g	14 (10-30) days

*In children: weight-adjusted dosage
**Treatment for *multiple EM* as for *acute LNB*
*** *in chronic LNB iv Tx recommend*

[1] age-restricted use, not in pregnant or breast feeeding women
[2] alternative Tx for children and pregnant or breast feeding women who are allergic to penicillin
[3] other third-generation cephalosporines such as cefotaxime also effective

Level of Evidence and Recommendation

Level of Recomm	IDSA/ILADS	AAN/EFNS
A	Strong evidence in favor of TX	Established as effective (at least 2 consistent Class I trials)
B	Moderate evidence in favor of TX	Probably effective (at least 1 Class I or 2 Class II trials)
C	Poor evidence in favor of TX	Possibly effective (at least 1 Class II or 2 Class III trials)

IDSA/ILADS	Level of Evidence	AAN/EFNS	Trial/ class
At least 1 properly randomized trials	I	Prospective, randomized, controlled study, masked outcome	I
At least 1 well-designed clinical trials, unrandomized, cohort or case-controll studies	II	Prospective, matched group cohort study, masked outcome	II
Oppinions of authorities based on clinical experience or descriptive studies	III	All other controlled trials (natural history controls, patients serve as own controls	III
	-	Uncontrolled studies, case series, case reports, expert oppinions	IV

IDSA: Infectious Disease Society of America; ILADS: International Lyme and associated Disease Society
AAN: American Academy of Neurology; EFNS: European Federation of Neurological Societies

Standard treatment for early LNB (adults)

Drug	Dosage	Duration	Recommendation/Evidence IDSA	AAN	EFNS
Ceftriaxone	2g/d iv	2 wks (10-28 ds)	B-I	B	B*
Penicillin G	4x5 MU/d iv	2 wks (10-28 ds)	B-I	B	B
Cefotaxime	3x2 g/d iv	2 wks (10-28 ds)	B-I	B	B
Doxycycline	100 mg p.o. BID	2 wks (10-28 ds)	B-I	B **	B**
Amoxycillin#	500mg p.o. TID	2 wks (14-21 ds)	B-III	C	
Cefuroxime axetil#	500mg p.o. BID	2 wks (14-21 ds)	B-III	C	

* first line in patients with CNS manifestations (GPP)
** for patients without symptoms or signs of CNS involvement (GPP)
# in patients with normal CSF or without signs for meningitis when doxycycline is contraindicated

Standard treatment for chronic # and late CNS-LNB (adults)

Drug	Dosage	Duration	Recommendation/Evidence IDSA	AAN	EFNS
Ceftriaxone	2g/d iv	2 - 4 weeks	B-II	„parenteral treatment recommended“	GPP (3 weeks)
Penicillin G	4x5 MU/d iv	2 - 4 weeks	B-II*		
Cefotaxime	3x2g/d iv	2 - 4 weeks	B-II*		

Chronic LNB must not be confused with „Chronic Lyme“ as defined by ILADS
* in children B-III
GPP: good practice point

- Response to Tx in chronic LNB may be slow and incomplete
- **More than 4 weeks of Tx are not recommended**
- **Re-Tx is not recommended unless relapse is shown by reliable objective measures**

Tx of early LNB in Europe: follow-up (≥ 1y)

Trial	n	Diagnosis	Design	Antibiotic Tx	Duration	Follow-up	Re-Tx	Outcome	Rel/Progr
Krüger 1990				P (70%)				62% free of symptoms	0/0
Hansen 1992									0/0
Hammers-Berggren 1993									0/0
Karlsson 1994									0/0
Treib 1998									?/?
Karkkonen 2001									0/0
Berglund 2002									0/0
Vrethem 2002									?/?
Kaiser 2004									0/0
Ljostad 2010	85	(64 definite, 21 possible)	Random. Prospect.	C or D	14 ds	1 ys	0	16,5% objective findings 31,5% subjective symptoms	0/0
Skogman 2012	84	Confirmed LNB (children)	Prospect., controlled	C (52%); P (8%); D (40%)	10-14 ds	5 (3-8) ys	0	19% objective definitive sequelae 8% possible sequelae.	0/0

Σ=909

- No progression to late LNB after standard antibiotic Tx
- Normalization of CSF pleocytosis
- Residua and/or subjective symptoms in up to 50% of patients

*Generally recommended duration Tx-duration for LNB in Sweden: : 10-21d. Rez/Progr: relapse/progression; Random.: randomized; cc: cell count; P: penicillin-G iv. 2x10 or 4x5 MioU daily, or 3-4x 3g daily; D: doxycycline 2x100mg p.o.; D iv: doxycylline iv. 200mg day 1-2,100mg day 3-10; C: ceftriaxone 2g iv. daily; Cefur: cefuroxime iv. 3x3g daily. d: day; m: month; y: year; cc: cell count.

Tx of late LNB in Europe: follow-up

Trial	n	Dg	Duration pre Tx	Antibiotic Tx	Duration	Follow-up	Outcome	Re-Tx	Rel/Progr
Ackermann 1985	1/							s Tx)	0/0
Weder 1987	5								0/0
Ackermann 1988	4								?/0
Kohler 1988	4								0/0
Krüger 1991	9								0/0
Hansen 1992	1								0/0
Karlsson 1994	4								0/0
Kaiser 2004	1							s x)	0/0
Σ=									

- No further progression after standard antibiotic Tx
- Clinical improvement and normalisation of CSF pleocytosis slower than in early LNB
- Objective residua frequent

P: penicillin-G iv. 20-24 MioU daily, or 3-4x 3g daily; D: doxycycline 2x100mg p.o.: C: ceftriaxone 2g iv. daily; Cefur: cefuroxime iv. 3x3g daily; DP benzylpenicillin benzathin 1MioU im.; D iv: doxycycline iv. 200mg daily; A: amoxicillin 2,25g p.o. daily ; A iv: amoxicillin iv. 4x1g daily; Cefotax: cefotaxime iv. 3x2g daily. Rez/Progr: relapse/progression; random.: randomized; cc: cell count; n.m. not mentioned; d: day; m: month; y: year.

Persistent or reappearing subjective symptoms in post-Tx-LB due to:

- Selection of persons with „Medically unexplained symptoms“? *(Seltzer et al 2000)*
- Postinfectious sequelae as known from other infections? *Hickie et al 2006*
- Autoimmune phenomena? *(Chandra et al 2010)*
- Psychiatric comorbidity? *(Hasset et al 2008)*
- Diagnostic error? *(Seidel et al 2007)*

or

- Chronic persistent infection? ⟹ „Chronic Lyme“ *(Cameron 2004)*

[affords in the view of ILADS prolonged or repeated courses of antibiotic-Tx until symptoms disappear (antibiotic maximalism)]

Yet, the majority of symptoms used in ILADS-guidelines are non-specific and without any dg. benefit

Symptoms of Lyme disease

- Fatigue
- Low grade fevers, 'hot flashes' or chills
- Night sweats
- Sore throat
- Swollen glands
- Stiff neck
- Migrating arthralgias, stiffness and, less commonly, frank arthritis
- Myalgia
- Chest pain and palpitations
- Abdominal pain, nausea
- Diarrhea
- Sleep disturbance
- Poor concentration and memory loss
- Irritability and mood swings
- Depression
- Back pain
- Blurred vision and eye pain
- Jaw pain
- Testicular/pelvic pain
- Tinnitus
- Vertigo
- Cranial nerve disturbance (facial numbness, pain, tingling, palsy or optic neuritis)
- Headaches
- 'Lightheadedness'
- Dizziness

Cameron D et al. Expert Rev Anti Infect Ther. 2004;2(1 Suppl):S1-13

Tx-trials on PLDS

Trial	Patients/Controls	Regimen/primary endpoint	Results	SAD
Klempner et al 2001	78 seropositive and 51 seronegative pts with PLDS	C for 30 ds followed by D for 60 ds (n=64) or placebo (n=60) Improvement on SF-36 score at d 180	Intention-to-treat analyses at d 30, 90 and 180: **no difference** between verum and placebo, seropositive and seronegative, and between combined groups	**Two pts*:** SAD associated with treatment (hospitalization)
Krupp et al 2003	55 pts with persistent severe fatigue after LB	C (n=28) or iv. placebo (n=24) for 28 ds Improvement in fatigue score (FSS-11) and cognitive function, CSF Osp-A at 6 ms	**Improvement in fatigue** (22% vs. 9%) but no benefit in cognition, no reduction of CSF Osp-A	**Four pts*:** SAD associated with treatment (hospitalization)
Fallon et al 2007	37 pts with objective memory impairment and at least 3 ws of previous iv. antibiotic Tx	2:1 randomization: C (n=23) or iv. placebo (n=14) for 10 ws Improvement at w 12 and w 24 (neurocognitive performance)	Slightly greater improvement in the antibiotic group at week 12, but **not at week 24**	**Seven pts:** withdrew from therapy (AE), cholecystectomy (one patient)
Cameron 2008	84 pts with recurrence of symptoms after successful Tx	A for 3 ms (n=52) vs. placebo (n=34) SF-36 QOL PCS and MCS at m 6	**Improvement of QOL**: 46% (verum) vs. 18% (placebo) p=0,007	No SAD; Herxheimer: in 10% of A-, in 9% of placebo-group

C: ceftriaxone 2g iv. once daily; D: doxycycline 2x100mg p.o. daily; A: amoxicillin 3g p.o. daily; SAD: serious adverse events; w: week; m: month; d: day; pts: patients; vs.: versus. * 1,6% resp. 7,7% potentially life-threatening

Tx-trials on PLDS

Trial	Comments
Klempner et al 2001	• Not adjusted for baseline levels • MCID too high
Krupp et al 2	nts
Fallon et al 2	red
Came 2008	onth 3 • Seropositivity status ignored

- No benefit, or ambigous benefit outweighed by Tx-associated risks in 3 NIH sponsored class I RCTs
- Improvement of QOL in one prospective placebo-controlled trial of low quality

Difference between IDSA and ILADS guidelines

Condition	Evidence for recomendation	
	IDSA	ILADS
Retreatment	None	A-II
Prolonged antibiotics	None	A-II
Combination Tx	None	B-III
Empiric Tx	None	B-III
Evidence for recommendation: A: good; B: moderate.		
Quality of data: II: ≥1 well designed clinical trial without randomization; III: expert opinion.		

Cameron D et al. Expert Rev Anti Infect Ther. 2004

„The ILADS guidelines are poorly constructed and do not provide a sound evidence-based approach to the diagnosis and care of patients with LB“

Independent Appraisal of ILADS 2004 „Evidence-based guidelines for the management of Lyme disease“; UK-Health Protection Agency, 8 Dec.2010 [http://www.hpa.org.uk]

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Summary

- No class I Tx-trials for active LB
- 2-4 weeks course of ß-lactam antibiotics or tetracyclines is an effective standard Tx of LB (level B recommendation)
- Chronic LNB, a well defined and clearly diagnosable syndrome, responds to standard antibiotic Tx
- „Chronic Lyme “ is not formally defined. It is used as synonym for chronic infection in different contexts
- PLDS refers to subjective symptoms lasting > 6 months after standard Tx of LB
- No evidence for overall benefit of prolonged antibiotic Tx of PLDS (class I trials)
- „Antibiotic maximalism“ in Tx of LB is not based on evidence and potentially harmful