Attachment 3: Appendix

Numbers in brackets refer to reference list in the article.

Appendix 1

Feder's criteria for "presumptive chronic Lyme disease"

Feder et al. have described 4 clinical categories to which patients with presumptive "chronic Lyme borreliosis" can be assigned [142]:

(1) Symptoms of an unknown cause without evidence of infection with *Borrelia burgdorferi*. In this category a combination of non-specific complaints is assumed to be a strong indication of "chronic Lyme borreliosis" [243]. However, the non-specific symptoms are found in about 10% of the normal US population regardless of whether the region is endemic to Lyme borreliosis or not [169], [170].
(2) Symptoms of a known, well-defined disease without evidence of infection with *Borrelia burgdorferi*. Here, the original diagnosis is presumed to be false (e.g. multiple sclerosis).
(3) Symptoms of an unknown cause and serology results that are positive for Lyme borreliosis, but no objective clinical findings of Lyme borreliosis now or in the past.
(4) Post-treatment Lyme disease syndrome (PTLDS). Cf. Section 4.3 and Appendix 2.

Appendix 2

The Infectious Diseases Society of America (IDSA) recommended the following diagnostic criteria for PTLDS in 2006 [27]

(1) Previous, confirmed Lyme borreliosis (according to CDC criteria) and regression or stabilisation of objective symptoms of Lyme borreliosis under a generally accepted antibiotic treatment regimen.
(2) Onset of subjective symptoms (fatigue, extensive musculoskeletal pain, cognitive disorders) within 6 months after diagnosis of Lyme borreliosis and persistence of symptoms (or chronic recurrent onset) for at least 6 months after completion of antibiotic treatment.
(3) The subjective symptoms lead to a relative impairment of daily activities.
(4) Exclusion criteria:

- Active, untreated co-infection
- Objective findings during physical examination or neuropsychological testing that explain the symptoms
- Subjective symptoms that were present before the Lyme borreliosis
- Another underlying disease that explains the symptoms (e.g. morbid obesity, sleep apnoea, narcolepsy, autoimmune diseases, drug side effects, (insufficiently treated or decompensated) cardiopulmonary diseases, endocrine diseases, malignant diseases within the last 2 years, liver diseases, depressive disorders, bipolar diseases, delusional disorders, dementia, eating disorders, drug or alcohol abuse within the last 2 years
- Laboratory and/or imaging findings that could explain the symptoms (e.g. BSG>50mm/h, abnormal serum levels for thyroid hormone, total protein, immunoglobulins, liver values, calcium, phosphorus, urea, electrolytes, creatinine. Abnormal urine test results.

Appendix 3

Table 6

Absolute results and forms of manifestation from the 8 RCTs and 8 cohort studies (modified according to [4])

Study (RCT)	Case definition	Manifestation	Neurological residual symptoms after 3–12 months	
			Doxycycline	Beta lactam antibiotics
Ljostad 2008 [226]	Definite (n=71) Possible (n=31)	Early manifestations (Bannwarth's syndrome, cranial nerve paresis, radiculopathies) n=97 (95%) Late manifestations (myelopathy, ACA with paraesthesia, encephalopathy) n=5 (5%)	28/54 (52%)	32/48 (66%) (Ceftriaxone)
Karlsson 1994 [221]	Probable	Not differentiable, predominantly early manifestations	6/31 (19%)	4/21 (19%) (Penicillin G)
Kohlhepp 1989 [246]	Possible	Early manifestations (radiculopathy, meningitis, cranial nerve paresis)	19/39 (49%)	23/36 (63%) (Penicillin G)
Study (RCT)	**Case definition**	**Manifestations**	**Neurological residual symptoms after 12 months**	
			Doxycycline	**Beta lactam antibiotics**
Ljostad 2008 [226]	Confirmed (n=71) Possible (n=31)	See above	22/44 (50%)	19/41 (46%)
Karlsson 1994 [221]	Probable	See above	3/30 (10%)	3/21 (14%)
Kohlhepp 1989 [246]	Possible	See above	12/39 (30%)	11/36 (30%)

Study (RCT)	Case definition	Manifestations	Neurological residual symptoms after >3 months	
			Cefotaxime	Penicillin G
Hassler 1990 [229]	Possible	Early manifestations (radiculopathies)	14/49 (28%)	24/44 (54%)
Pfister 1989 [228]	3/21 Possible 19/21 Patients confirmed/ probable	Early manifestations (Bannwarth's syndrome, meningitis)	2/11 (18%)	2/10 (20%)

RCT without relevant data for a defined comparison			
Study (RCT)	**Case definition**	**Manifestations**	
Oksi 1988	Possible	Not differentiable, predominantly early manifestations	
Pfister 1988 [245]	3/21 Possible 18/21 Probable	Early manifestations (Bannwarth's syndrome)	
Pfister 1991 [227]	6/30 Possible 24/30 Confirmed/probable 24/30 Confirmed /probable	Early manifestations (Bannwarth's syndrome)	

Appendix 4

Table 7

Frequency of side effects from 6 RCTs (modified according to [4])

Beta lactam vs. doxycycline					
Design	**Studies**	**Beta lactam group**	**Doxycycline group**	**Side effects beta lactam**	**Side effects doxycycline**
RCTs	2	79	88	32 (40%)	25 (28%)
NRS	2	47	75	1 (2%)	5 (7%)
Penicillin vs. cefotaxime					
Design	**Studies**	**Cefotaxime group**	**Penicillin G group**	**Side effects cefotaxime**	**Side effects penicillin G**
RCTs	2	80	79	39 (49%)	22 (28%)

Appendix 5

Table 8

Side effects from comparison studies (modified according to [4])

Individual side effects		
Beta lactam vs doxycycline	**Beta lactam**	**Doxycycline**
Ljostad, 2008 [226]	**n=56**	**n=57**
All AE	26	57
SAE	3 (cholecystitis/stomatitis/allergy)	1 (duodenal ulcer)
Other (not broken down by therapy)	diarrhoea n=17, nausea n=3, nausea + diarrhoea n=2, constipation n=9, exanthema n=3	
Karlsson 1994 [221]	**n=23**	**n=31**
AE	3 (dizziness n=1, thrombophlebitis n=2)	4 (exanthema n=2, diarrhoea n=2)
Berglund 2002 [164]	**n=18**	**n=39**
AE/SAE	0	0
Borg 2005 [247]	**n=29**	**n=36**
AE	1 (leucopenia)	5 (GI issues n=3, phototoxicity n=2)
Penicillin vs. cefotaxime	**Penicillin**	**Cefotaxime**
Hassler 1990 [229]	**n=69**	**n=69**
AE	20 (diarrhoea n=6, Herxheimer's reaction n=14)	37 (diarrhoea n=9, Herxheimer's reaction n=28)
SAE	n=2 (colitis, shock)	n=2 (colitis, allergic reaction)
Pfister 1989 [228]	**n=10**	**n=11**
AE	0	0

Appendix 6

Information for patients following a tick bite (from DDG S2k-LL Cutaneous Lyme Borreliosis; AWMF register no. 013/044) [1]

1. Remove the tick as quickly as possible. Special tick tweezers or tick cards are the best way to do this.
   Pull or push the tick slowly and patiently out of the skin – without twisting or pre-treating it with oil or glue. Avoid squishing the body.
   If some of the suction organ remains in the skin (often misinterpreted as the "head"), you can remove it with a sterile needle or a curette, or have it removed by a physician. If the suction organ remains in the skin, there is no danger of the Borrelia being transferred.
2. Carefully examine your body and especially the heads of children for more ticks.
3. Observe the skin near the site of the bite for 6 weeks. A redness that appears directly after the bite as a result of the tick's saliva will disappear within several days. If the redness reappears or if the original redness enlarges to ≥5 cm, be sure to consult a doctor. This can be a sign of erythema migrans (migrating rash), the early manifestation of Lyme disease.
4. When there is a typical migrating rash near the site of the bite, it should be treated with antibiotics, preferably with doxycycline (for children aged 9 and up) or amoxicillin, even when no blood test has been carried out or if no antibodies have been detected.
5. The dissemination of the Borrelia through the blood – even without a reddening of the skin – is noticeable by a flu-like feeling without respiratory symptoms. This may be a precursor to organ disease, e.g. of the joints or the nervous system. Consult a physician who will decide whether or not a blood screening for Borrelia antibodies is necessary.
6. Early-stage Lyme disease can be completely cured when antibiotic treatment is carried out in line with the guidelines. This also prevents late manifestations.
7. It is not necessary to examine the tick for Borrelia since a positive detection does not confirm whether the Borrelia were indeed transferred to the skin and whether, in the case of a transmission, this will lead to an infection. A negative result does not exclude the possibility of a transmission.
8. Only a small proportion of the people infected with Borrelia become ill! This is why a prophylactic treatment with oral antibiotics is not recommended.

Appendix 7

Frequency of clinical manifestations for neuroborreliosis from 3 studies

Table 9

Frequency of clinical manifestations for neuroborreliosis (Kaiser 2004 [42])

Clinical manifestation	Acute (early) neuroborreliosis N=86	Chronic (late) neuroborreliosis N=15
Radiculitis spinalis – Isolated radiculitis spinalis – Radiculitis spinalis et cranialis – Isolated radiculitis cranialis	– 73.2% – 38.4% – 34.9% – 20.9%	
Radiculitis cranialis – VII – II – III – VI	– 55.8% – 51.2% – 1.2% – 1.2% – 2.2%	
Myeloradiculitis	3.5%	
Cerebral vasculitis	1.2%	
Myositis	1.2%	
Encephalomyelitis		100%

Table 10

Frequency of clinical manifestations for neuroborreliosis (Hansen & Lebech 1992 [41])

Clinical manifestation at the time of diagnosis	Acute (early) neuroborreliosis N=176	Late neuroborreliosis N=11
Lymphocytic meningoradiculitis with mononeuritis (Bannwarth's syndrome)	61%	
Facial paresis, unilateral	37%	
Facial paresis, bilateral	17%	
Palsy, VI cranial nerve	5%	
Painful lymphocytic meningoradicultis (without paresis)	24.6%	
Subacute lymphocytic meningitis (without pain, without paresis)	4.8%	
Myelo-meningoradiculitis	3.7%	
Chronic lymphocytic meningitis (with paresis, duration of disease >6 months)		1.6%
Chronic progressive encephalomyelitis		4.3%

Table 11

Frequency of clinical manifestations for neuroborreliosis (Oschmann et al. 1998 [47])

Symptoms related to neuroborreliosis	N=330
Paresis, peripheral	45%
Paresis, central	9%
Sensory disorder, peripheral	44%
Sensory disorder, central	4%
Cranial nerve palsy, facial nerve	39%
Cranial nerve palsy, other	8%
Bladder paralysis	5%
Organic brain syndrome	3%
Parkinson syndrome	7%
Cerebellar ataxia	2%
Stroke	1.2%
Myositis	0.3%

Appendix 8

Table 12

GRADE ranking of studies on antibiotics (modified according to [4])

Quality assessment						Number of patients		Effects		Quality
Number of studies	Design	Risk of bias	Inconsis-tency	Indirectness	Imprecision			RR (95% CI)	Absolute	
Beta lactam vs. doxycycline						Beta lactam	Doxycycline			
Neurological symptoms after >4 months										
3	RCTs	Relevant[1]	No relevant inconsis-tencies	No relevant indirectness	Relevant[2]	59/105 (56.2%)	53/124 (42.7%)	RR 1.27 (0.98–1.63)	115 more per 1000 (from 9 fewer to 269 more)	Early manifestations: ++-- LOW Late manifestations: +--- VERY LOW (additional indirectness)
Side effects										
2	RCTs	Relevant[1]	No relevant inconsis-tencies	No relevant indirectness	Relevant[2]	24/80 (30%)	30/87 (34.5%)	RR 0.82 (0.54–1.25)	62 fewer per 1000 (from 159 fewer to 86 more)	Early manifestations: ++-- LOW Late manifestations: +--- VERY LOW (additional indirectness)

Neurological symptoms after >12 months										
3	RCTs	Relevant[1]	No relevant inconsis-tencies	No relevant indirectness	Relevant[2]	33/98 (33.7%)	37/113 (32.7%)	RR 0.98 (0.68–1.42)	7 fewer per 1000 (from 105 fewer to 138 more)	Early manifestations: ++-- LOW Late manifestations: +--- VERY LOW (additional indirectness)
[1]two unblinded studies, concerns regarding treatment allocation and selective reporting [2]limited number of cases										
Cefotaxime vs. penicillin						**Penicillin**	**Cefotaxime**			
Neurological symptoms after >4 months										
2	RCTs	Relevant[1]	No relevant inconsis-tencies	No relevant indirectness	Relevant[2]	26/54 (48.1%)	16/60 (26.7%)	RR 1.81 (1.1–2.97)	216 more per 1000 (from 27 more to 525 more)	Early manifestations: ++-- LOW Late manifestations: +--- VERY LOW (additional indirectness)
Side effects										
2	RCTs	Relevant[1]	Relevant[3]	No relevant indirectness	Relevant[2]	22/79 (27.8%)	39/80 (48.8%)	RR 0.56 (0.38–0.84)	215 fewer per 1000 (from 78 fewer to 32 fewer)	+--- VERY LOW
[1]high risk of bias [2]limited number of cases [3]no findings were reported in one study										

Combination of multiple antibiotics vs. single substance						Single substance	Combination			
Neurological symptoms										
2	Observa-tional study	Very serious[1]	No relevant inconsis-tencies	Relevant[2]	Relevant[3]	4/10 (40%)	2/8 (25%)	No pooling	No pooling	+--- VERY LOW
[1]high risk of bias [2]various types of interventions, different treatment periods [3]limited number of cases										
Antibiotic treatment vs. no treatment						**Treatment**	**No treatment**			
Neurological symptoms										
3	Observa-tional studies	Very serious[1]	No relevant inconsis-tencies	No relevant indirectness	Relevant[2]	30/94 (31.9%)	31/79 (39.2%)	No pooling	No pooling	+--- VERY LOW
[1]high risk of bias [2]limited number of cases										

Appendix 9

Table 13

Important differential diagnoses of Lyme neuroborreliosis

Neurological manifestation	Differential diagnoses	Clinical characteristics, lab findings
Facial paresis	Idiopathic facial paresis	– No CSF pleocytosis – Differentiation can be difficult in the early stage – especially with children
	Zoster oticus (Ramsay Hunt syndrome)	– Blisters on the outer ear canal (can be discrete or absent) and/or in the mouth – Pain close to the ear – Frequent hyperacusis and taste disorders – Virus detection from blisters and/or CSF – VZV AI
	Polyradiculitis cranialis (Miller Fisher syndrome)	– Rarely unilateral, barrier disorder – No CSF pleocytosis – GQ1b antibody – Involvement of further cranial nerves
	Traumatic facial paresis	– Patient history – Imaging
	Facial paresis with tumorous processes	– Cerebellopontine angle tumour – Parotid gland tumour – Meningeosis neoplastica: patient history (gradual progression) – CSF and imaging

Neurological manifestation	Differential diagnoses	Clinical characteristics, lab findings
	Mastoiditis, otitis media	– ENT results – Imaging
	Bacterial meningitis of another aetiology (incl. tuberculosis meningitis)	– CSF – Pathogen detection in CSF
	Sarcoidosis (Heerfordt syndrome)	– Facial swelling with parotid gland – Uveitis – Often bilateral facial paresis – Imaging – Serum marker for sarcoidosis
	Melkersson-Rosenthal syndrome	– Relapsing course – Geographic tongue – Facial swelling
Mono/polyradiculitis (Bannwarth's syndrome)	Mono/polyradiculitis from other pathogens: VZV, EBV, HSV, CMV (latter with immunosuppression)	– Pathogen detection in CSF
	Root compression from slipped disc, facet syndrome, sacroiliac joint syndrome, piriformis syndrome	– Symptoms depend on strain – Can be mechanically triggered locally (or trigger points) – Spinal imaging
	Spinal tumour (e.g. neurinoma, ependymoma); meningeosis neoplastica	– Gradual progression – Imaging
	Spondylodiscitis, spinal/epidural abscess	– Can be mechanically triggered locally – Inflammation parameters – Imaging

Neurological manifestation	Differential diagnoses	Clinical characteristics, lab findings
Meningitis	Chronic meningitis (caused by pathogen, not immunodeficiency): – Mycobacterium tuberculosis – Treponema pallidum – Mollaret meningitis (HSV2) – Parameningeal focus of infection (sinusitis, mastoiditis, otitis) – HSV 1 and 2 – Lymphocytic chorioretinitis – Enteroviruses – VZV (seldom)	Microbiological testing for pathogen in CSF
	Chronic meningitis (caused by pathogen, with immunodeficiency): – HIV – Mycobacterium tuberculosis – CMV – Cryptococcus neoformans – Candida spp. – Toxoplasma gondii	
	Chronic meningitis (not caused by pathogen): – Meningeosis neoplastica – M. Behcet – Collagenosis – Sarcoidosis – Migraines with CSF pleocytosis – Idiopathic steroid responsive chronic meningitis – Drug-induced meningitis – Leptomeningeal involvement in isolated CNS angiitis	– Microbiological differentiation of pathogen-induced cause in CSF and, if necessary, serum – Cerebrospinal fluid cytology – Autoimmune serology – Internal-rheumatological clarification – Drug history
Myelitis	Chronic myelitis (not caused by pathogen):	– Microbiological differentiation of pathogen-induced cause in CSF and, if necessary, serum – Spinal MRI

Neurological manifestation	Differential diagnoses	Clinical characteristics, lab findings
	– Chronic progressive multiple sclerosis – Neuromyelitis optica (NMO) and neuromyelitis optica spectrum disorders (NMOSD) – Collagenosis – Paraneoplastic – After vaccination (extremely rare)	– Autoimmune serology – Internal-rheumatological co-assessment – Vaccination history
	Myelitis (caused by pathogen): – Mycobacterium tub. – Treponema pallidum – HSV, VZV, enteroviruses If immunodeficiency is present: – HIV, CMV, JCV Parainfectious with: – Mycoplasma pneumoniae – HSV-2, VZV, CMV, EBV, adenovirus, ECHO, mumps	– Microbiological differentiation of pathogen-induced cause in CSF and, if necessary, serum – Spinal MRI
	Chronic myelopathy: – Spinal canal stenosis – Funicular myelosis (vitamin B12 deficiency) – Degenerative diseases (ALS, spastic spinal paralysis) – Spinal dural arteriovenous fistulas – Radiation myelopathy – Adrenoleukodystrophy – Hepatic myelopathy – Copper deficiency myelopathy – HIV myelopathy – Spinal tumours – Alcoholic myelopathy	– Spinal imaging (MRI, CT, myelography, angiography) – Extended lab testing – Internal clarification – CSF for differentiation from an infectiological cause – Electrophysiology (EPs)

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German Society of Neurology (DGN)
German Dermatology Society (DDG)
German College of General Practitioners and Family Physicians (DEGAM)
German Society for Occupational and Environmental Medicine (DGAUM)
German Society of Oto-Rhino-Laryngology, Head and Neck Surgery (DGHNOKHC)
German Society for Hygiene and Microbiology (DGHM)
German Society for Immunology (DGfI)
German Society of Infectious Diseases (DGI)
German Society of Cardiology and Cardiovascular Research (DGK)
German Society of Paediatrics and Adolescent Medicine (DGKJ)
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The German Association of Psychiatry, Psychotherapy and Psychosomatics (DGPPN)
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German Society of Rheumatology (DGRh)
German Pain Society (DGSS)
German Ophthalmological Society (DOG)
Paul Ehrlich Society for Chemotherapy (PEG)
Robert Koch Institute

The following organisations have not approved the guideline:
German Borreliosis Society (DBG)
Action Alliance Against Tick-Borne Infections Germany (OnLyme-Aktion)
Borreliosis and FSME Association Germany (BFBD)
German Federal Association for Tick-Borne Diseases (BZK)