

## DBG Objections to the IDSA Lyme Guidelines (24 Apr. 2009)

The Deutsche Borreliose-Gesellschaft (German Society of Lyme-Borreliosis) raises objections to the IDSA Lyme Guidelines published in 2006. The fundamental basis for our objections is that the implementation of the IDSA guidelines extends beyond the United States and into Europe. Accordingly, our ability to diagnose and treat patients with Lyme disease is being severely restricted by these guidelines, and we believe that the guidelines must be revised to provide greater flexibility in the diagnosis and treatment of Lyme disease given the poor laboratory test sensitivity, the persistence of the organism despite adherence to IDSA protocols, and the seriousness of this illness.

We are raising objections to the following guideline recommendations:

**Challenge to Lab Diagnostic Test Requirement--Page 1090** :*“Diagnostic testing performed in laboratories with excellent quality-control procedures is required for confirmation of extracutaneous Lyme disease....”*

**Challenge to Restrictions on the Use of Clinical Judgment—Pages 1089-90** : *“Clinical findings are sufficient for the diagnosis of erythema migrans, but clinical findings alone are not sufficient for diagnosis of extracutaneous manifestations of Lyme disease or for diagnosis of HGA or babesiosis.”*

### **Challenge to Persistence--Page 1118**

**The Basis for Treatment Limitations for Early and Late Lyme Disease and Post-Lyme Syndrome:** “The notion that symptomatic, chronic *B. burgdorferi* infection can exist despite recommended treatment courses of antibiotics (tables 2 and 3) in the absence of objective clinical signs of disease, is highly implausible as evidenced by (1) the lack of antibiotic resistance in this genus [39, 40, 310], (2) the lack of correlation of persistent symptoms with laboratory evidence of inflammation or with the eventual development of objective physical signs [223, 257, 288, 289], and (3) the lack of precedent for such a phenomenon in other spirochetal infections [315–317]. Additional compelling evidence against the hypothesis that persistent symptoms are the result of persistent infection is the fact that the concentrations of antibodies against *B. burgdorferi* in many of these patients diminish to undetectable levels [257, 286, 288, 318]. The panel is unaware of any chronic infection in which antibody titers diminish despite persistence of the causative organism. In syphilis, patients who are regarded as having treatment failure typically have persistent or rising titers of antibodies [319]. Finally, Lyme disease lacks characteristics of other infections that justify longer treatment courses, such as infections in immunodeficient hosts, infections in which a pathogen is inhibited but not killed by antimicrobial therapy or in which available antimicrobials are minimally active in vitro, infections caused by an intracellular pathogen, infections involving a biofilm, infections on a heart valve, or infections involving a clinical site in which there is ischemia, a foreign body, a sequestrum, or frank pus [170]. The ‘cystic’ forms of *B. burgdorferi* that have been seen under certain growth conditions in vitro have not been shown to have any clinical significance [320].”

**Challenge to Restriction on Specific Therapeutic Options--Recommendation 5, Page 1105** : *“Because of a lack of biologic plausibility, lack of efficacy, absence of supporting data, or the potential for harm to the patient, the following are not recommended for treatment of patients with any manifestation of Lyme disease: first generation cephalosporins, fluoroquinolones, carbapenems, vancomycin, metronidazole, tinidazole, amantadine, ketolides, isoniazid, trimethoprim-sulfamethoxazole, fluconazole, benzathine*

*penicillin G, combinations of antimicrobials, pulsed-dosing (i.e., dosing on some days but not others), long-term antibiotic therapy, anti-Bartonella therapies, hyperbaric oxygen, ozone, fever therapy, intravenous immunoglobulin, cholestyramine, intravenous hydrogen peroxide, specific nutritional supplements, and others (see table 4) (EIII)."*

**Late Neurologic Lyme Disease--Recommendation 3, Page 1113:** "Adult patients with late neurologic disease affecting the central or peripheral nervous system should be treated with ceftriaxone (2 g once per day intravenously for 2–4 weeks) (tables 2 and 3) (B-II). Cefotaxime or penicillin G administered intravenously is an alternative (B-II). *Response to treatment is usually slow and may be incomplete. Re-treatment is not recommended unless relapse is shown by reliable objective measures.* Ceftriaxone is also recommended for children with late neurologic Lyme disease (tables 2 and 3) (B-II). Cefotaxime or penicillin G administered intravenously is an alternative (B-III)."

**Post Lyme Disease Syndrome Definition—Recommendation 1, Page 1120:** *There is no well-accepted definition of post-Lyme disease syndrome. This has contributed to confusion and controversy and to a lack of firm data on its incidence, prevalence, and pathogenesis. In an attempt to provide a framework for future research on this subject and to reduce diagnostic ambiguity in study populations, a definition for post-Lyme disease syndrome is proposed in table 5. Whatever definition is eventually adopted, having once had objective evidence of B. burgdorferi infection must be a condition sine qua non.* Furthermore, when laboratory testing is done to support the original diagnosis of Lyme disease, it is essential that it be performed by well-qualified and reputable laboratories that use recommended and appropriately validated testing methods and interpretive criteria [117, 118]. Unvalidated test methods (such as urine antigen tests or blood microscopy for detection of *Borrelia* species) should not be used [337].

**Post Lyme Disease Syndrome Treatment Limitation—Recommendation 2, Pages 1120-1121:** To date, there is no convincing biologic evidence for the existence of symptomatic chronic *B. burgdorferi* infection among patients after receipt of recommended treatment regimens for Lyme disease. *Antibiotic therapy has not proven to be useful and is not recommended for patients with chronic (6 months) subjective symptoms after administration of recommended treatment regimens for Lyme disease (E-I).*

Our objections relate to diagnosis and treatment of Lyme disease (LD), chronic Lyme borreliosis (LB) and the so-called "post-Lyme syndrome" (PLS).

#### 1. Objections to the IDSA guidelines for diagnosis of LD and chronic LB:

- Seronegativity is frequent in LD and does not rule out a chronic persistent *Borrelia burgdorferi* (Bb) infection (1-18).
- The differential diagnosis between multiple sclerosis and neuroborreliosis based on CSF and serum analysis is not possible in at least 25% of cases (9-11, 21).
- Peripheral neuropathy is not rare but occurs in over 20% of LD cases (22-25).

- So-called two-tier testing is not suitable to diagnose LB, particularly in the late phase, for the following reasons:
  - o The test methods available on the market are not standardized with respect to their diagnostic value.
  - o The sensitivity of ELISA and IFA screening tests varies from 50% to 70%.
  - o The sensitivity of the Lyme Western blot is around 10% higher than that of the screening test.
  - o This difference in sensitivity means that there is a risk that the screening test will be negative whereas the Western blot shows positive, and the diagnosis of LD will be missed.
  - o Neither the screening test nor the Western blot can rule out infection with Bb, i.e., there is a problem of seronegativity (based on the screening test and Western blot) even though the illness persists and has been confirmed by identification of the pathogenic agent (1-18).

## 2. Objections to the IDSA guidelines for treatment of LD and chronic LB:

- In Europe, LD is often associated with generalized dissemination throughout the entire body, including involvement of the central nervous system (CNS). Treatment should therefore be carried out with antibiotics that penetrate the CNS, irrespective of the various manifestations of the illness (arthritis, neuroborreliosis, neuropathy, acrodermatitis, carditis, encephalopathy).
- The oral antibiotics recommended by IDSA, namely low-dose doxycycline, amoxicillin and cefuroxime, do not penetrate the CNS; in contrast, minocycline, gemifloxacin and intravenous third-generation cephalosporins yield high concentrations in CSF above the minimal inhibitory concentration (MIC) for Bb (19).
- Contrary to the negative opinion of IDSA, the following antibiotics and methods of treatment have proven to be advantageous: carbapenems, ketolides and gemifloxacin (19); pulsed-dosing (20).

- The antibiotic treatment of EM displays a therapeutic failure rate of at least 10% (15, 41, 45, 47, 67-74).
- Bb could still be identified in the skin even after multiple antibiotic treatments with ceftriaxone, doxycycline and cefotaxime (47-49).
- The resistance of Bb to numerous antibiotics has been proven (61).

### 3. Objections to the proposed IDSA definition of “post-Lyme syndrome”:

- Antibiotic treatment according to the IDSA guidelines does not guarantee elimination of Bb.
- Subjective complaints may reflect ongoing infection with Bb rather than a different illness (PLS).
- The disease situation described by Steere et al (26) as “minor signs and symptoms” and by Bujak (27) as “post-Lyme syndrome” represents serious discomfort for affected patients that is comparable to decompensated cardiac insufficiency, degenerative joint diseases, pronounced diabetes mellitus or a condition after a myocardial infarction according to Klempner et al (2).
- The following facts suggest the existence of chronic LB due to persistent Bb infection:
  - o Persistent symptoms of LB with Bb identification despite intensive antibiotic treatment (28-46).
  - o Members of the Deutsche Borreliose Gesellschaft have documented 150 such cases (ISBN 978-3-640-19378-3, submitted for publication).
  - o There is an extensive body of literature on the existence of chronic LB (45, 50-55).
  - o Bb could be cultured in every stage of chronic LB (28-44), even after intensive antibiotic treatment (20, 41, 56-60).

- Numerous publications deal with chronic LB and the problems with its antibiotic treatment (20, 48-49, 62-66).
- There is a high therapeutic failure rate for the antibiotic treatment of LB in its late phase (52, 54-56, 65, 75-77).
- The so-called (according to the IDSA guidelines) adequate antibiotic therapy is subject to these restrictions:
  - Since Bb can possibly resist various antibiotics (including those recommended by the IDSA guidelines) switching antibiotics may be indicated (61).
  - While Bb may be resistant to erythromycin, related antibiotics appear to be suitable for treatment of LB (26, 83-85).
  - Duration of treatment depends on the organic manifestations, severity and course of disease, as outlined in numerous references (2, 20, 25-26, 41, 45-47, 49, 51, 53-54, 56, 60-66, 71-73, 75, 86-94).

## References

1. Kalish RA et al, Persistence of Immunoglobulin M or Immunoglobulin G Antibody Responses to *Borrelia burgdorferi* 10-20 Years after Active Lyme Disease, *Clinical Infectious Diseases* (2001), 33: 780-5
2. Klempner M et al, Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease, *N Engl J Med* (2001), 345: 85-92
3. Dejmekova H et al, Seronegative Lyme arthritis caused by *Borrelia garinii*, *Clinical Rheumatology* (2002), 21(4): 330-4
4. Tylewska-Wierzbanowska S, Chmielewski T, Limitation of serologic testing for Lyme borreliosis: evaluation of ELISA and western blot in comparison with PCR and culture methods, *Wien Klin Wochenschr* (2002), 114(13-14): 501-5
5. Breier F et al, Isolation and polymerase chain reaction typing of *Borrelia afzelii* from a skin lesion in a seronegative patient with generalized ulcerating bullous lichen sclerosus et atrophicus, *Br J Dermatol* (2001), 144(2): 387-392
6. Wang P, Hilton E, Contribution of HLA alleles in the regulation of antibody production in Lyme disease, *Front Biosci* (2001), 6:B10-B16
7. Grignolo MC et al, Reliability of a polymerase chain reaction (PCR) technique in the diagnosis of Lyme borreliosis, *Minerva Med* (2001), 92(1): 29-33
8. Honegr K et al, Persistence of *Borrelia burgdorferi sensu lato* in patients with Lyme borreliosis, *Epidemiol Mikrobiol Immunol* (2001), 50(1): 10-6
9. Eldoen G et al, Lyme neuroborreliosis in More and Romsdal, *Tidsskrift for Den Norske Lægeforening* (2001), 121(17): 2008-11
10. Wilke M et al, Primarily chronic and cerebrovascular course of Lyme neuroborreliosis: case reports and literature review, *Arch Dis Child* (2000), 83(1): 67-71
11. Bertrand E et al, Central nervous system infection caused by *Borrelia burgdorferi*. Clinicopathological correlation of three post-mortem cases, *Folia Neuropathol* (1999), 37(1): 43-51
12. Oksi J et al, *Borrelia burgdorferi* detected by culture and PCR in clinical relapse of disseminated Lyme borreliosis, *Annals of Medicine* (1999), 31(3): 225-32
13. Aberer E et al, Heterogeneity of *Borrelia burgdorferi* in the skin, *American Journal of Dermatopathology* (1996), 18(6): 571-9
14. Luft BJ et al, Azithromycin compared with amoxicillin in the treatment of erythema migrans. A double-blind, randomized, controlled trial, *Annals of Internal Medicine* (1996), 124(9): 785-91
15. Mursic VP et al, Formation and cultivation of *Borrelia burgdorferi* spheroplast L-form variants, *Infection* (1996), 24(3): 218-26
16. Coyle PK et al, Detection of *Borrelia burgdorferi*-specific antigen in antibody negative cerebrospinal fluid in neurologic Lyme disease, *Neurology* (1995), 45: 2010-2014
17. Häupl T et al, Persistence of *Borrelia burgdorferi* in ligamentous tissue from a patient with chronic Lyme borreliosis, *Arthritis & Rheumatism* (1993), 36(11): 1621-6
18. Nadelman RB et al, Isolation of *Borrelia burgdorferi* from the blood of seven patients with Lyme disease, *American Journal of Medicine* (1990), 88: 21-6

19. Hunfeld K-P et al, Standardized in vitro susceptibility testing of *Borrelia burgdorferi* against well-known and newly developed antimicrobial agents – Possible implications for new therapeutic approaches to Lyme disease, *Int J Med Microbiol* (2002), 291 (suppl 33): 125-137
20. Hassler D et al, Pulsed high dose cefotaxime therapy in refractory Lyme borreliosis, *Lancet* 338 (1991), 193 (Letter)
21. Keller TL et al, PCR detection of *Borrelia burgdorferi* DNA in cerebrospinal fluid of Lyme neuroborreliosis patients, *Neurology* (1992), 42(1):32-42
22. Kindstrand E et al, Polyneuropathy in late Lyme borreliosis – a clinical, neurophysiological and morphological description, *Acta Neurol Scand* (2000), 101(1):47-52
23. Halperin JJ, Lyme disease and the peripheral nervous system, *Muscle Nerve* (2003), 28(2):133-43
24. Kristoferitsch W, *Neuropathie bei Lyme-Borreliose*, Springer Verlag Wien/New York, 1989
25. Asch ES et al, Lyme Disease: An Infectious and Postinfectious Syndrome, *The Journal of Rheumatology* (1994), 21:3
26. Steere AC et al, Treatment of early manifestations of Lyme Disease, *Ann Intern Med* (1983), 99:22-26
27. Bujak DI et al, Clinical and neurocognitive features of the post Lyme syndrome, *J Rheumatol* (1996), 23(8):1392-7
28. Johnson RC, Isolation techniques for spirochetes and their sensitivity to antibiotics in vitro and in vivo, *Rev. Infect. Dis.* (1989) 11 Suppl 6: 1505-10
29. Asbrink E, Hovmark A, Successful cultivation of spirochetes from skin lesions of patients with erythema chronicum migrans afzelius and acrodermatitis chronica atrophicans, *Acta pathol. Microbiol. Immunol. Scand. Sect.* (1985), B 93: 161-163
30. Preac-Mursic V et al, European *Borrelia burgdorferi* isolated from humans and ticks culture conditions and antibiotic susceptibility, *Zentralbl. Bakteriol. Mikrobiol. Hyg.* (1986), A 263(1-2): 112-8
31. Pfister HW et al, Latent Lyme neuroborreliosis: Presence of *Borrelia burgdorferi* without concurrent inflammatory signs, *Neurology* (1989) 39: 1118-1120
32. Nadelmann RB et al, Isolation of *Borrelia burgdorferi* from the blood of seven patients with Lyme disease, *Am. J. Med.* (1990), 88: 21-26
33. Nadelmann RB et al, Detecting *Borrelia burgdorferi* in blood from patients with Lyme disease, *J. Infect. Dis.* (1994), 169 (6): 1410-1
34. Berger BW et al, Cultivation of *Borrelia burgdorferi* from the blood of two patients with erythema migrans lesions lacking extracutaneous signs and symptoms of Lyme disease, *J. Am. Acad. Dermatol* (1994), 30 (1): 48-51
35. Goodman JL et al, Bloodstream invasion in early Lyme disease: results from a prospective, controlled, blinded study using the polymerase chain reaction, *Am. J. Med* (1995), 99(1): 6-12
36. Koning J de, Hoogkamp-Korstanje JA, Diagnosis of Lyme disease by demonstration of spirochetes in tissue biopsies, *Zentralbl. Bakteriol. Mikrobiol. Hyg.* (1986), A. 263(1-2): 179-88

37. Koning J de et al, Demonstration of spirochaetes in patients with Lyme disease with a modified silver stain, *J. Med. Microbiol.* (1987) 23(3): 261-7
38. Koning J de et al, Demonstration of spirochetes in cardiac biopsies of patients with Lyme disease, *J. Infect. Dis.* (1989), 160(1): 150-3
39. Stanek G et al, Isolation of *Borrelia burgdorferi* from the myocardium of a patient with longstanding cardiomyopathy, *N. Engl. J. Med.* (1990), 322(4): 249-52
40. Schmidli J et al, Cultivation of *Borrelia burgdorferi* from joint fluid three month after treatment of facial palsy due to Lyme borreliosis, *J. Infect. Dis.* (1988), 158: 905-906
41. Preac-Mursic V et al, Survival of *Borrelia burgdorferi* in antibioticly treated Patients with Lyme Borreliosis, *Infection* (1989), 17: 355-359
42. Häupl T et al, Persistence of *Borrelia burgdorferi* in ligamentous tissue from a patient with chronic Lyme borreliosis, *Arthritis Rheum.* (1993), 36(11): 1621-6
43. Johnston YE et al, Lyme Arthritis. Spirochetes found in synovial microangiopathic lesions, *Am. J. Pathol.* (1985), 118: 26-34
44. Weber K et al, Spirochetes isolated from two patients with Morphaea, *Infection* (1988), 16: 25-26
45. Phillips SE et al, A proposal for the reliable culture of *Borrelia burgdorferi* from patients with chronic Lyme disease, even from those previously aggressively treated, *Infection* (1998), 26(6):364-7
46. Kleemann, W et al, Prolonged antibiotic therapy in PCR confirmed persistent Lyme disease, submitted to *Future Drugs*, Expert Review of antiinfective therapy
47. Steere AC, Lyme-Disease, *New Engl. J. Med.* (1989), 321: 586-596
48. Dattwyler RJ et al, Treatment of late Lyme-Borreliosis – Randomised comparison of Ceftriaxone and Penicillin, *Lancet*, (1988a) 1191-1194
49. Hassler D et al, Cefotaxime versus penicillin in the late stage of Lyme disease – prospective, randomized therapeutic study, *Infection* (1990) 18(1): 16
50. Brorson O, Brorson SH, An in vitro study of the susceptibility of mobile and cystic forms of *Borrelia burgdorferi* to hydroxychloroquine, *Int. mikrobiol* (2002), 5: 25-31
51. Sigal LH, Treatment of Lyme Disease, UpToDate 2006
52. Logigian EL et al, Chronic neurologic manifestations of Lyme disease, *N. Engl. J. Med.* (1990), 323: 1438-1444
53. Logigian EL et al, Successfull Treatment of Lyme Encephalopathy with iv. Ceftriaxone, *J. infect. Dis.* (1999), 180: 377-383
54. Ziska MH et al, Physician Preferences in the Diagnosis and Treatment of Lyme Disease in the United States, *Infection* (1996) 24 No. 2, MMV Medizin Verlag GmbH, München, 1996
55. Asch ES et al, Lyme Disease: Ann. Infectious and Postinfectious Syndrome, *J. Rheumatol.* (1994), 21: 454-456
56. Hassler D, Langzeitbeobachtungen zum Krankheitsbild der Lyme-Borreliose in einem Endemiegebiet, Habilitationsschrift Universität Erlangen (1997)
57. Koning J de, Histopathologic Aspects of Lyme Borreliosis, Groningen (1995), 145 S., Selbstverlag



58. Kraiczy P et al, Mechanism of complement resistance of pathogenic *Borrelia burgdorferi* isolates, *Intern. Immunopharmacol* (2001), 1: 393-401
59. Kraiczy P et al, Immune evasion of *Borrelia burgdorferi*; Insufficient killing of the pathogen by complement and antibody, *Int. J. Med. Microbiol.* (2002), 291: 141-146 (Suppl.33)
60. Duray PH, Steere AC, Clinical pathologic correlations of Lyme disease by stage. In: *Lyme disease and related disorders*, *Ann. NY Acad. Sci.*, (1988), 539: 65-79
61. Hunfeld K-P et al, In vitro susceptibility testing of *Borrelia burgdorferi* sensu lato isolates cultured from patients with erythema migrans before and after antimicrobial chemotherapy, *Antimicrob Agents Chemother.* (2005), 49(4): 1294-301
62. Hassler D, Cefotaxim in der Behandlung der chronischen Lyme-Borreliose, *Fortschr. Antimicr. Antineopl. Chemother.* (1992) 11:109-118
63. Hassler D, Maiwald M, Zweimalige Re-Infektion mit *Borrelia burgdorferi* bei einem immunkompetenten Patienten, *Dtsch Med Wochenschr* (1994), 119: 338-42
64. Liu NY et al, Randomized trial of doxycycline vs. amoxicillin/probenecid for the treatment of Lyme arthritis: treatment of non responders with iv penicillin or ceftriaxone, *Arthritis Rheum.* (1989), 32: 46
65. Steere AC et al, Treatment of Lyme Arthritis, *Arthritis & Rheumatism* (1994), 37: 878-888
66. Halperin JJ, Abnormalities of the nervous System in Lyme Disease: Response to antimicrobial Therapy, *Rev. of Inf. Dis.*, Vol II, Sppl. 6 (1989), 1499-1504
67. Steere AC, Seronegative Lyme disease, *JAMA* (1993), 270(11): 1369
68. Weber K et al, A randomized Trial of Ceftriaxone versus Oral Penicillin for the Treatment of Early European Lyme Borreliosis, *Infection* (1990), 18: 91-96
69. Weber K et al, Clinical features of Lyme Borreliosis, In: Weber K, Burgdorfer W: *Aspects of Lyme Borreliosis*, Springer-Verlag, Heidelberg (1993), 93-104
70. Strie F et al, Azithromycin versus doxycycline for treatment of erythema migrans: clinical and microbiological findings, *Infection* (1993), 21(2): 83-8
71. Manning PG, Fulminant refractory Lyme disease, *Iowa Med* (1989), 79:277-80
72. Gasser R et al, Cases of Lyme borreliosis resistant to conventional treatment: improved symptoms with cephalosporin plus specific beta-lactamase inhibition, *Microb Drug Resist* (1995), 1:341-4
73. Limbach FX et al, Treatment resistant Lyme arthritis caused by *Borrelia garinii*, *Ann Rheum Dis* (2001), 60:284-6
74. Thanassi WT, Schoen RT, The Lyme disease vaccine: conception, development, and implementation, *Ann Intern Med* (2000), 132:661-668
75. Dattwyler RJ et al, Treatment of late Lyme disease, *Lancet* (1988), 1: 1191-4
76. Dattwyler RJ et al, Treatment of late Lyme disease – a comparison of 2 weeks vs 4 weeks of ceftriaxone, VII International Congress of Lyme Borreliosis, San Francisco (1996), abstract D662
77. Steere AC et al, The spirochetal etiology of Lyme disease, *N Engl J Med* (1983), 308:733-40

78. Goettner G et al, Improvement of Lyme borreliosis serodiagnosis by a newly developed recombinant immunoglobulin G (IgG) and IgM line immunoblot assay and addition of VlsE and DbpA homologues, *J Clin Microbiol* (2005), 43(8):3602-9
79. Bingnan MA et al, Serodiagnosis of Lyme Borreliosis by Western Immunoblot: Reactivity of Various Significant Antibodies against *Borrelia burgdorferi*, *Journal of Clinical Microbiology* (1992), 30(2):370-376
80. Tilton RC et al, The Western Immunoblot for Lyme Disease: Determination of Sensitivity, Specificity, and Interpretive Criteria with Use of Commercially Available Performance Panels, *Clin Infect Dis* (1997), 25(Suppl1):31-4
81. Aguero-Rosenfeld ME et al, Diagnosis of Lyme Borreliosis, *Clinical Microbiology Reviews* (2005), 484-509
82. Lomholt H et al, Long-term serological follow-up of patients treated for chronic cutaneous borreliosis or culture-positive erythema migrans, *Acta Derm Venereol* (2000), 80(5):362-6
83. Hansen K et al, Roxithromycin in Lyme borreliosis: discrepant results of an in vitro and in vivo animal susceptibility study and a clinical trial in patients with erythema migrans, *Acta Dermatologica Venerologica* (1992), 72:297-300
84. Oschmann P, Kaiser R, Therapy and prognosis. IN: Oschmann P et al: Lyme borreliosis and tick-borne encephalitis, UNI-Med Verlag AG (1999b), International Medical Publishers, Bremen, Germany, pp. 112-119
85. Wormser GP et al, Practice guidelines for the treatment of Lyme disease, The Infectious Diseases Society of America, *Clin Infect Dis* (2000), 31(Suppl. 1):1-14
86. Dattwyler RJ et al, Ceftriaxone as effective therapy in refractory Lyme disease, *J Infect Dis* (1987), 155:1322-5
87. Oksi J et al, Comparison of oral cefixime and intravenous ceftriaxone followed by oral amoxicillin in disseminated Lyme borreliosis, *Eur J Clin Microbiol Infect Dis* (1988), 17(10):715-9
88. Fallon BA et al, A randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy, *Neurology* (2007), 10(Epub ahead of print)
89. Massengo SA et al, Severe neuroborreliosis: The benefit of prolonged high-dose combination of antimicrobial agents with steroids- - an illustrative case, Department of Neurology, Centre Hospitalier de Mont de Marsan, 40000 Mont de Marsan, France
90. Kaplan R et al, Cognitive function in post-treatment Lyme disease: do additional antibiotics help?, *Neurology* (2003), 60:1916-1922
91. Krupp I et al, Study and treatment of post Lyme disease (STOP-LD): a randomized double masked clinical trial, *Neurology* (2003), 60:1923-1930
92. Pfister HW et al, Randomized comparison of ceftriaxone and cefotaxime in Lyme neuroborreliosis, *J Infect Dis* (1991), 163(2):311-8
93. Kohlhepp W et al, Treatment of Lyme borreliosis. Randomized comparison of doxycycline and penicillin, *J Neurol* (1989), 236:464-69
94. Gasser R und Dusleag J, Oral treatment of late Lyme borreliosis with roxythromycine plus co-trimoxazole, *Lancet* (1990), 1189-90