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Survival of Borrelia burgdorferi in Antibiotically Treated Patients with Lyme borreliosis

Summary: The persistence of *Borrelia burgdorferi* in patients treated with antibiotics is described. The diagnosis of Lyme disease is based on clinical symptoms, epidemiology and specific IgG and IgM antibody titers to *B. burgdorferi* in serum. Antibiotic therapy may abrogate the antibody response to the infection as shown in our patients. *B. burgdorferi* may persist as shown by positive culture in MKP-medium; patients may have subclinical or clinical disease without diagnostic antibody titers to *B. burgdorferi.* We conclude that early stage of the disease as well as chronic Lyme disease with persistence of *B. burgdorferi* after antibiotic therapy cannot be excluded when the serum is negative for antibodies against *B. burgdorferi.*

Zusammenfassung: *Persistenz der Borrelia burgdorferi bei negativer Serologie und Behandlung mit Antibiotika.* Es wird über die Persistenz von *Borrelia burgdorferi* bei sechs Patienten berichtet. Nach dem Zecken- bzw. Insektenstich und Erythema migrans konnte *B. burgdorferi* noch Wochen nach der Antibiotikatherapie nachgewiesen werden. Serologische Befunde waren außer bei einem Patienten negativ. Diese Ergebnisse bestätigen unsere früheren Beobachtungen und sprechen dafür, daß die Antibiotikabehandlung die Antikörperbildung gegen *B. burgdorferi* beeinflussen kann. Ferner zeigen diese Ergebnisse und Beobachtungen, daß nicht nur im Frühstadium der Lyme Borreliose, sondern auch in chronischen Stadien bzw. bei Persistenz des Erregers der Nachweis von Antikörpern negativ bleiben kann.

Introduction

Lyme borreliosis (LB), a multisystem disorder with skin, neurological, cardiac and arthritic symptoms caused by *Borrelia burgdorferi* and predominantly transmitted in Europe by infected ticks, *Ixodes ricinus,* can be diagnosed by the detection of antibodies to *B. burgdorferi* and isolation of the borreliae. The therapy of Lyme borreliosis, especially in the late chronic stage seems to be problematic. Antimicrobial therapy with penicillin G and tetracycline has been recommended. Various treatments especially with penicillin G have been proposed and practiced but none of them has been uniformly effective [1–6]. The last time the cephalosporins, cefotaxime and ceftriaxone have been used with success. We report here about survival of *B. burgdorferi* in patients with Lyme borreliosis after therapy with antibiotics.

Patients and Methods

Patients: Clinical data of our patients are listed in Table 1.
Serological tests: Antibodies to the *B. burgdorferi* in blood and cerebrospinal fluid (CSF) were determined by indirect immunofluorescence test (IFT) as described previously [7]. To avoid unspecific false positive reactions, the test samples were absorbed with *Treponema phagedenis.* Antibody titers ≥ 1:64 are regarded as significantly elevated, titers of 1:32 as borderline.
Bacteriological examinations: The samples of CSF and skin biopsies were examined for *B. burgdorferi* by darkfield microscopy and by culture in MKP-medium as previously described [8]. The cultures were incubated at 33 °C for 5 weeks and examined weekly by darkfield microscopy and subcultures.

Results

Spirochetes were isolated from the culture of CSF and skin biopsy specimens from six patients. The isolates showed typical protein pattern of *B. burgdorferi* in SDS-page. The results concerning the relapse of the disease and reinfection with *B. burgdorferi* after penicillin G and tetracycline therapy in the first case are presented in Figure 1.
Case 1: On July 7, 1985, a five-year-old boy had erythema migrans behind the left ear that faded after three days. A tick bite had never been seen by the parents. Beginning July 25, he had fever of up to 39.4 °C, was more tired than usually and had an erythema in the face, on his upper back and on the upper arms. On August 8 he was admitted to a community hospital with a temperature of 37.9 °C and meningism. CSF analysis showed a lymphocytic pleocytosis (480 cells/µl) and an increase in total protein (86 mg/dl): the electroencephalogram (EEG) was abnormal. Serum IgG and IgM antibody titers against *B. burgdorferi* were 1:64 and 1:128, respectively. Borrelia antibodies were not detected in CSF; culture for *B. burgdorferi* isolation from CSF was not done. The patient was treated with penicillin V orally in a dose of 100,000 U/kg daily for 14 days. On September 2 the CSF contained 26 cells/µl, the protein concentration was 40 mg/dl.
Beginning September 7, a paresis of the left facial nerve appeared that faded almost completely after two weeks. In the CSF, cells increased to 285/µl and protein concentration to 111mg/dl. He then received doxycycline orally in a

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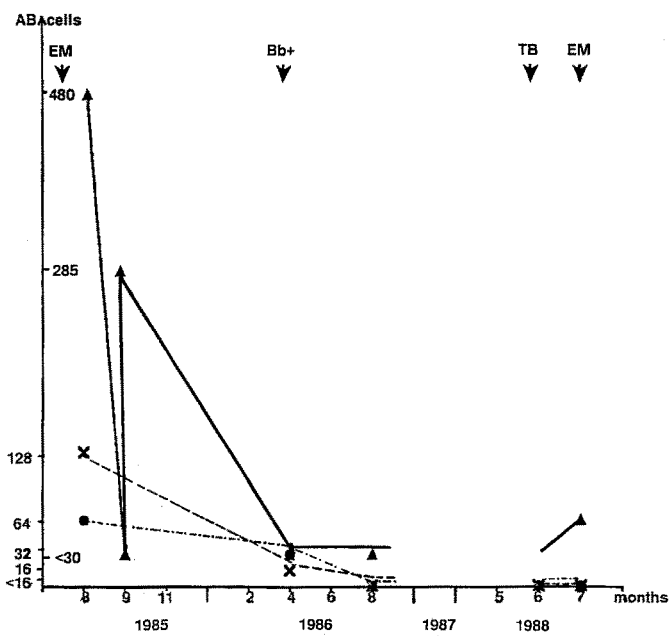
Table 1: Patients with survival of *Borrelia burgdorferi* after antibiotic therapy.

Patient/ diagnosis	Therapy until isolation of *Borrelia burgdorferi*	Culture +	Antibody titer at time of culture + Serum IgG	IgM	CSF
1. LMR-Bannwarth	Penicillin V 100,000 U/kg – 14 days Doxycycline 2 mg/kg day – 10 days	CSF 7 months a.t.	1:32	1:16	<2
2. LMR-Bannwarth	Penicillin G 20 million U/daily – 10 days	CSF 3 months a.t.	1:32	1:64	<2
3. LMR-Bannwarth	Ceftriaxone 2 g/day – 10 days	CSF 7.5 months a.t.	n.d.		
4. Erythema migrans	Penicillin V 3 million U/daily – 12 days	Skinbiopsy 3 months a.t.	1:128	1:16	
5. Erythema migrans	Penicillin G 10 million U/day – 10 days	Skinbiopsy 2 months a.t.	1:32	<1:32	
6. Erythema migrans	Doxycycline 200 mg/day – 10 days	Skinbiopsy 1 month a.t.	<1:16	<1:16	

a.t. = after therapy; n.d. = not done.

dose of 2mg/kg/daily for 10 days. The CSF gradually became normal, but the EEG was abnormal during falling asleep. In April 1986, the boy had a relapse with tiredness, fever, vomiting, headache and meningism. A new tick bite had not been noted, erythema migrans was missing. The CSF contained only 20 cells/µl und total protein was 35 mg/dl. Antibody titers against *B. burgdorferi* were in serum IgG 32, IgM 16 and in CSF IgG and IgM <2. EEG was again abnormal. *B. burgdorferi* was isolated from CSF after 4 weeks incubation in MKP-medium. The patient was now treated with penecillin V orally in a dose of 200,000 U/kg daily for 22 days. After that CSF protein, cells and electroencephalogram were normal. Cultures for *B. burgdorferi* isolation were not done after the second penicillin V treatment. The IgG and IgM immunofluorescent assay performed in August 1986 was negative in serum and CSF.



AB Antibody titers against *Borrelia burgdorferi*
● – · – · IgG
x – – – IgM
▲ — Cells
EM Erythema migrans
TB Tick bite
Bb+ *Borrelia burgdorferi* culture positive

Figure 1: Persistence of *Borrelia burgdorferi* and reinfection after therapy with penicillin V and tetracycline.

In 1988, the patient had a new attack. Two weeks after a tick bite, he had an erythema migrans around the bite site and a painful meningoradiculitis. CSF analysis showed a light lymphocytic pleocytosis (39 cells/µl). *B. burgdorferi* antibody titers in serum and CSF were negative. Culture for *B. burgdorferi* isolation from CSF was not done.

Case 2: A 49-year-old male presented an erythema migrans on the malleolus, 3 days after an insect bite. Typical clinical signs of LMR-Bannwarth syndrome with severe radicular pain and lymphocytic pleocytosis in CSF (144 cells/µl) and increase in total protein (68 mg/dl) began about 7 weeks after the insect bite. EEG was normal. The antibody titers against *B. burgdorferi* in serum at this time were positive (IgG 1:64, IgM 1:256); antibodies were not determined in CSF. Culture for *B. burgdorferi* isolation from CSF was not done.

The patient was treated with penicillin G i.v. in a dose of 20 million U daily over 10 days.

Laboratory investigation of CSF, 4 days after therapy revealed 66 cells/µl and 53 mg/dl protein. Serum IgG antibody titers against *B. burgdorferi* were positive (1:128), the IgM titer was still elevated (1:64). Intrathecal IgG antibody production was demonstrated by significantly elevated CSF/Serum Index (4.2). Culture for *B. burgdorferi* from CSF was not done. Neurological examination was normal, the patient was free of complaints.

Three months later the effect of antibiotic therapy was controlled and neurological examination and CSF examination for white blood cells and total protein were normal.

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Antibody titers against *B. burgdorferi* in serum were IgG 1:32, IgM 1:64 and in CSF negative (<1:2) The patient was free of complaints. However, when CSF was cultivated in MKP-medium, *B. burgdorferi* could be isolated.

Case 3: A 26-year-old patient was admitted to our hospital because of headache and intense radicular pain. The radicular pain was most severe at night and located bilaterally in the region of the dermatoma S1 and C7. She reported multiple bites by horseflies a few weeks prior to the admission. Neurological examination was completely normal. Lumbar puncture revealed a lymphocytic pleocytosis with 451 cells/µl. Both total protein (77 mg/dl) and the CSF/serum albumin ratio (10.7) were elevated. Oligoclonal IgG bands were not detected in the CSF. The diagnosis of Bannwarth's syndrome was made although antibodies to *B. burgdorferi* were not detected in serum or CSF. She received ceftriaxone, 2 g/day i.v. for 10 days. During antibiotic therapy, radicular pain and headache improved. Lumbar puncture for the determination of the CSF ceftriaxone concentration was made on the 10th day of therapy 3½ h after antibiotic infusion. The CSF ceftriaxone concentration as measured by HPLC was 1.45 mg/l. At follow-up examination, 7.5 months after antibiotic therapy, the patient reported recurrent episodes of radicular pain, headache, arthralgias and fever. Neurological examination was normal. Antibodies to *B. burgdorferi* were not detected. Repeated lumbar puncture revealed normal values for cell counts (1 cell/µl), total protein (24 mg/dl) and CSF/serum albumin ratio (1.9). Oligoclonal IgG bands were not detected. However, *B. burgdorferi* was isolated from the CSF after 6 weeks incubation in MKP-medium. Erythrocyte sedimentation rate (10/30) and leucocyte counts (7,100/mm^3) were normal; C reactive protein, rheumatoid factor and antinuclear antibodies were negative. The patient was treated with cefotaxime 3 × 2 g/day i.v. for 14 days.

Case 4: This, 44-year-old man noticed an erythema migrans of 2 months' duration on the right thigh on June 1, 1988. He had no complaints. His IgG and IgM antibody titers against *B. burgdorferi* were 1:128 and < 1:16, respectively; *B. burgdorferi* could be isolated from skin biopsy taken from the border of the erythema migrans. Treatment carried out with phenoxymethyl-penicillin, 1 million U/3 times daily for 12 days. Erythema migrans disappeared within 2 weeks after the penicillin therapy. Three months later the IgG and IgM antibody titers against *B. burgdorferi* had normalized but *B. burgdorferi* was again isolated from skin biopsy adjacent to the scar of the first biopsy. There were no later manifestations in this otherwise healthy man who could be observed for 7 months. He then received ceftriaxone. Three months after retreatment with ceftriaxone (2 g daily/21 days) a second control culture from a skin biopsy performed adjacent of the first scars was negative.

Case 5: A 40-year-old man developed erythema migrans 24 days after a tick bite, which was slightly pruritic and located on the right arm. Besides a mild itching in the area of the lesion, fatigue and headache, the patient was asymptomatic. The patient received 1 × 10 million U penicillin G for 10 days starting 5 weeks after the tick bite. The erythema migrans faded about 12 days later. Serum IgG and IgM antibody titers against *B. burgdorferi* were negative, cultures for borrelia isolation were not done. Suffering from headache and fatigue 2 months after the disappearance of erythema migrans and 4 months after the tick bite, the patient went to see a doctor. At that time low titre (IgG 1:32, IgM < 1:32) antibodies to *B. burgdorferi* were detected. At our recommendation a skin biopsy of the tick bite area, showing no sign of erythema migrans, was taken. The presence of *B. burgdorferi,* was demonstrated by culturing the organisms in MKP-medium 2 months and 2 weeks after the therapy.

Case 6: On October 20, 1987, a 60 year-old-woman claimed to have had a slowly expanding asymptomatic skin eruption for at least 6 months. There was no history of a tick bite. She had been taking methylprednisolone 4 mg daily for asthma bronchiale for years. In September 1987, she received doxycycline, 200 mg daily for 10 days from her family physician because of a common cold. Physical examination on October 20, 1987, revealed an erythema migrans 32 by 20 cm around both groins. She experienced occasional attacks of palpitations and dizziness, but had been suffering from angina pectoris for years. IgM and IgG antibody titers against *B. burgdorferi* were negative. *B. burgdorferi* could be isolated from skin biopsied from the edge of the erythema migrans on October 20, 1987. ESR and immunoglobulins were normal. The patient refused to take another antibiotic.

Discussion

It is well known that erythema migrans, the most characteristic sign of Lyme borreliosis, tends to disappear without therapy. Nevertheless, antibiotic treatment with penicillin or tetracycline has been recommended in order to prevent subsequent clinical manifestations of Lyme borreliosis [1–6, 20].

Use of penicillin for treatment of Lyme borreliosis was initiated in Europe on the basis of empiric evidence. Therapy today is founded on experiences and studies concerning the favorable effect of penicillin and tetracycline conducted by *Steere* et al. and *Weber* [1–4].

However, some patients later developed symptoms of the disease despite antibiotic treatment [9–11]. Because of these observations it has become questionable if a definite eradication of *B. burgdorferi* with antibiotics is possible. In this context some results of our *in vitro* and *in vivo* studies concerning the susceptibility of *B. burgdorferi* to antibiotics may be of interest [12, 13]. Testing 20 strains of *B. burgdorferi* the MIC_{90} for penicillin G was found to be 4 mg/l. The corresponding result for tetracycline was 0.5 mg/l. These results confirm findings of other researchers [14, 15].

To kill 50% of *B. burgdorferi* with 1.0 µg of antimicrobials we required 48 h using penicillin G and 6–18 h using tetracycline. These differences should be taken into considera-

tion in the therapy of the disease. These results show that effective antibiotic therapy is not only dose dependent, the length of treatment and kind of antimicrobials can be of great importance.

In our *in vivo* experiments with gerbils we could not produce an erythema using intradermal (i.d.) or subcutaneous (s.c.) inoculations. However, we were able to isolate *B. burgdorferi* from the skin biopsy taken 4 cm from the injection site up to 8 months after the infection. The persistence of *B. burgdorferi* can exist in animal tissue and organs for one year and longer. *B. burgdorferi* could be isolated in infected control animals not treated with any antibiotics as well as in animals after treatment with penicillin G (320 mg/kg/day). In contrast, we did not find *B. burgdorferi* in infected animals treated one week with tetracycline (200 mg/kg/day), azithromycin (8 mg/kg/day), imipenem (36 mg/kg/day) and cephalosporins.

Cephalosporins showed a much better antiborrelial effect than penicillin. The highest antiborrelial activity can be seen in the cefotaxime group, the most effective substances were cefotaxime and ceftriaxone.

According to the data of recent clinical studies the cephalosporins are more efficient than penicillin G in late [16, 17], but not in early Lyme borreliosis [21]. *Dattwyler* et al. [17] and *Pal* et al. [11] reported that ceftriaxone and cefotaxime were effective in treating patients with meningoencephalitis and late borreliosis who did not respond to penicillin G therapy.

The CSF concentrations of penicillin G and cefotaxime in our study cefotaxime versus penicillin G [18] demonstrate that cefotaxime penetrates to a greater extent than penicillin G. The CSF levels are evidently above the MIC_{90} values which we determined for *B. burgdorferi.* The concentration of penicillin G did not reach the MIC_{90} in any of our patients.

Data from controlled clinical studies are still scanty, clinical experience is based mostly on a short observation time. Furthermore, proof of a successful therapy is based not only on the disappearance of clinical symptoms but also on the elimination of *B. burgdorferi* and proof is difficult to achieve.

Here we demonstrate the persistence of *B. burgdorferi* in CSF and skin after the therapy with the penicillin G, penicillin V, tetracycline and ceftriaxone. Surprisingly, the isolation of *B. burgdorferi* was possible from the CSF 3–8 months and from skin biopsy 3 months after the antibiotic therapy and disappearance of erythema migrans. Persistent borrelia infection of the CSF was demonstrated by us in a patient with Bannwarth syndrome from the preantibiotic era 10 weeks after the tick bite [19]. In skin biopsy of a treated patient with ACA *B. burgdorferi* could be isolated 3 years after therapy [20]. In untreated patients we demonstrated the presence of *B. burgdorferi* 7 months after the tick bite and 4 months after disappearance of erythema migrans.

In all our treated patients a second – repeated tick – or other insect bite had never been seen, an erythema migrans was not observed. The lack of repeated insect bite and erythema migrans, negative AB-titer against *B. burgdorferi* and negative CSF examination suggest persistence of *B. burgdorferi* rather than reinfection.

How often *B. burgdorferi* may persist in the CSF or skin after therapy or its effect in producing atypical manifestations of disease is not known. The isolation of *B. burgdorferi* from CSF and skin biopsy in our patients after antibiotic therapy with normal CSF-values and negative serological tests for *B. burgdorferi* raises important considerations in the treatment of Lyme borreliosis.

The current recommended penicillin therapeutic regimens would not be expected to assure borreliacidal levels in the CSF as shown by clinical data and our posttreatment isolation of *B. burgdorferi.*

Very interesting is the recurrent episode 7.5 months after ceftriaxone therapy in case no. 3. The antibiotic concentration on the 10th day of the therapy (2 g daily i.v./10 days) 3.5 h after infusion was 1.45 mg/l (MIC_{90} = 0.06 mg/l). Repeated lumbar puncture 7.5 months after therapy revealed normal cell counts, normal total protein and CSF/serum albumin ratio and neurological examination. However, *B. burgdorferi* was isolated from CSF in culture. The reason for the persistence of *B. burgdorferi* in patients after the treatment with antimicrobials is not completely understood. A number of factors may be concerned i.e. stage of disease, virulence of *B. burgdorferi,* insufficient antibiotic therapy, microbial persistence by reduced antibiotic sensitivity and possibility of *B. burgdorferi* survival in tissue, especially in brain tissue and in certain types of cells.

The capacity of *B. burgdorferi* to hide in tissue (heart muscle, eyes, brain) and an insufficient tissue penetration of antibiotics are critical for therapy. Clinical stage of the disease or where *B. burgdorferi* may be present, in heart muscle, eyes or brain, or if there is a uniform pattern, is still unknown.

The central nervous system invasion by spirochetes and a persistence of *Treponema pallidum* after penicillin G therapy is common in neurosyphilis [22, 23].

In view of the hitherto failure of treatment, low CSF concentration of penicillin G, survival of *B. burgdorferi* in patients treated with antibiotics, the moderate penicillin G susceptibility of the organism and unpredictable progression of the disease, it seems appropriate to treat patients with substantially larger doses of antibiotics and/or longer than is provided in present treatment regimens.

Early administration of antibiotics and a 3 to 4 week treatment with 200 mg/daily of doxycycline or 2 g of amoxycillin (stage 1), 3 × 2 g/daily of cefotaxime or 1 × 2 g/daily of ceftriaxone (stages 2 and 3) could probably eliminate the risk of relapse and progression of the disease. Penicillin G cannot be recommended generally, however, if used ≥ 20 million units daily for several weeks are needed. Finally, the effect of therapy ought to be controlled individually by antibody-titer and *B. burgdorferi* culture. As shown, negative antibody-titers do not provide evidence for successful therapy; antibody-titers may become negative despite persistence of *B. burgdorferi.*

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Erratum

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E. Ulrich et al.: "Comparative Efficacy of Ciprofloxacin, Azlocillin, Imipenem/Cilastatin and Tobramycin in a Model of Experimental Septicemia Due to Pseudomonas aeruginosa in Neutropenic Mice", page 311.
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