Contribution to the topic of *Borrelia burgdorferi* sensu lato

Dear Editor,

In this issue of *Orvosi Hetilap*, PROF. NEUBERT *et al* published a paper titled "The *in vitro* antibiotic susceptibility of *Borrelia burgdorferi* sensu lato". In their *in vitro* studies, the authors demonstrated beyond doubt the efficacy of, otherwise impairing, ciprofloxacin, along with its bactericidal property. By inhibiting bacterial DNA gyrase, ciprofloxacin interferes with the replication and transcription of the genetic material of this microbe [5]. However, according to personal communication by PROF. NEUBERT, when administered as monotherapy, ciprofloxacin is not sufficiently effective for the treatment of Lyme borreliosis.

Resulting from my previous *in vitro* experiments, I was the first to publish data – one to three years ahead of the workgroups of BARBOUR, GARON, and NEUBERT – on the role of DNA gyrase in the microorganism *B. burgdorferi* sensu lato [1]. The inhibition of DNA gyrase possibly explains the therapeutic effect of ciprofloxacin administered as a component of antibiotic combinations [2, 3].

The conclusion of this study by HENNEBERG & NEUBERT underlines the need for combination therapy. More than a decade earlier, I had stated the following. *"Supposing that the antibiotic monotherapy of Lyme borreliosis is most controversial – as endorsed currently by all stakeholders involved in the debate – in order to achieve complete recovery, it is necessary to administer combination medication therapy, as well as to support the action of conventional antibiotics by the add-on use of agents that prevent the adaptation of the pathogen"* [1, 3].

Based on my hypothesis resulting from research conducted, as early as in 1990 I stated that **a precondition to the successful therapy of Lyme borreliosis** was to prevent the continuous change of the genetic material. Moreover, simultaneously, metabolic processes and should be stalled, leading at the same time to preventing bacterial cell wall synthesis, as well as the pathogen should be destroyed within the intracellular compartment.

Borrelia burgdorferi sensu lato is characterized by an unusual genetic polymorphism. This pathogen is capable of repeated genetic variations during the course of the disease it has caused. Accordingly, the destruction of the genetic material of the pathogen is essential to effective therapy. As shown by my studies, fluoroquinolones – which damage the genetic material – enhance the effects of the former on the pathogens of Lyme borreliosis by one or two magnitudes through synergies [1].

My original observation from *in vitro* studies is that when acting on the *Borrelia burgdorferi* sensu lato strain, **fluoroquinolones exert a post-antibiotic effect**. This explains why the symptoms can recur 10 to 18 days after the conclusion of combination therapy including ciprofloxacin. This transient deterioration of clinical status may last for a couple of days. Having sustained damage to their genetic material and incapable of multiplying, the spirochetes disintegrate, and their released components cause recurring symptoms. These account for the 2- to 3-week-long generation cycle of of the post-antibiotic effect as well as *Borrelia burgdorferi* sensu. The post-antibiotic effect provides *in vivo* evidence for the action of fluoroquinolones on the subphyla of this bacterial strain.

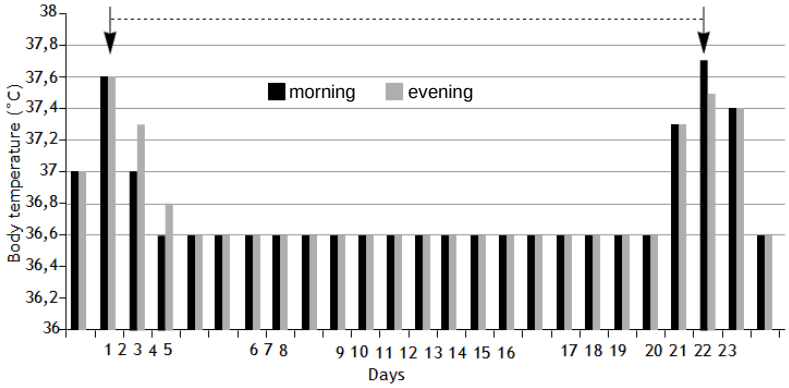

Figure 1. The fluctuation of symptoms in Lyme borreliosis, as reflected by the data of a seropositive patient. The periodic increases of body temperature were accompanied by a headache and articular pain. The clinical symptoms reveal the generation cycle of the pathogen, which is at least 2 to 3 weeks in the case of *Borrelia burgdorferi*

The cyclic variation in the number of pathogens observed during experimental infections also exhibits similar, periodic changes [8]. Furthermore, several-day long persistence and worsening of the symptoms occur during the clinical course of untreated Lyme borreliosis (*Figure 1*). The patient may even be symptom-free during the subclinical periods between these exacerbations.

Based on our observations and on the literature, we can assume that the optimum duration of treatment is two to three weeks. Concerning facultative intracellular pathogens, the duration of treatment should be twice as long – that is, four to six weeks – in order for the therapy to be effective.

Lyme borreliosis is a systemic, **complex disorder** affecting the entire body. Depending on the nature of the clinical symptoms, its diagnosis and treatment are the task of multiple medical specialties. During its chronic clinical course, Lyme borreliosis may be accompanied by any other disease. When this is the case, the diagnosis of this disease represents a truly consultational, differential diagnostic issue for all medical fields.

Evaluating the experience accumulated during the diagnosis and management of Lyme borreliosis, the American College of Physicians concluded that establishing the diagnosis is largely dependent on the epidemiological and clinical information available on the patient. Moreover, these data lend considerable support to the laboratory detection of the disease. Their conclusion was also conceded by the Board of Reagents [4, 9] and the objective foundations for the consultative diagnosis of Lyme borreliosis were thus laid.

In my experience, in the case of Lyme borreliosis established based on clinical signs and a diagnostic evaluation:

- Confirmed seropositivity is equivalent to a positive diagnosis of the disease' symptoms;
- Active processes reflected by the symptoms render a treatment necessary.

With regard to diagnostics, I would like to emphasize that treatment is required only when the clinical symptoms indicate active processes. In general, seropositive, but symptom-free patients should only be monitored. However, treatment may nevertheless be needed in the presence of severe stress or of accompanying diseases, because, according to our repeated experience, Lyme borreliosis may recur under these circumstances. In patients with an accompanying bacterial infection, the therapy selected for Lyme borreliosis should be adjusted to cover both conditions. In our follow-up studies conducted to date, the existence of a 'serological scar' – i.e. symptom-free seropositivity – could be demonstrated in only three recovered patients. Nevertheless, the presence of IgM-type antibodies is of diagnostic value and meaningful when establishing the diagnosis in patients with chronic disease. In fact, this phenomenon indicates the decline and insufficiency of host defenses. Recovery is characterized by slow, progressive reversion to seronegativity.

The targeted antibiotic therapy of Lyme borreliosis is not yet feasible. In addition to considering *in vitro* antimicrobial susceptibility, the appropriate drug should be chosen by taking into account the antibiotics the patient has been taking in recent years. When planning the therapeutic regimen, it is important to ascertain whether the administered antibiotics have had any impact on the clinical manifestations of Lyme borreliosis. In addition to taking this '**antibiotic history**', it would be expedient to identify the subphylum – or possibly subphyla – of the *B. burgdorferi* sensu lato strain [5] causing the disease, as this could yield further clues to choosing the appropriate antibiotic.

Based on the experience available so far and on data from the literature, it is reasonable to recommend that the antibiotics be administered in combinations and in doses sufficient to destroy a facultative intracellular, genetically polymorphous pathogen with a notoriously high mutation rate. Dosing should be individualized and guided by laboratory monitoring.

In view of the prolonged duration of the antibiotic therapy, **vitamin and trace mineral supplementation** is indispensable. Further, the patient should be warned of the need for strict adherence to hygienic measures. Replenishing the gut flora with *Lactobacilli* is recommended both during the course and after the end of antibiotic therapy; this is useful also for relieving enteric symptoms. Supportive treatment would be necessary to enhance the weakened systemic immune responses; however, no suitable medicinal products are available for this purpose. Lyme borreliosis is a chronic disease, which may inflict direct damage to the structures responsible for psychical functions and, in some cases, personality change dysfunctions may ensue. Therefore, the diagnosis and treatment of Lyme borreliosis require time and patience. The only option for verifying the efficacy of the administered therapy is follow-up, which is a component also of the rehabilitation process required due to the chronic nature of the disease.

Our observations carried out since the time when Lyme borreliosis was first described in Hungary and our experience in the follow-up care process confirm the effectiveness of the antibiotics listed in Table 1.- [2]. According to our knowledge, the parenteral administration of clarithromycin may also be beneficial.

Figure 2 summarizes the clinical information accompanying the requests for serological testing during the 5-year follow-up – and re-treatment as necessary – of 250 patients managed in compliance with the diagnostic and therapeutic principles discussed above. These data confirm with certainty that it is possible to cure Lyme borreliosis with antibiotics. In our experience, however, when administered as monotherapy, no antibiotic on its own can fully eradicate the pathogen, *Borrelia burgdorferi* senso lato, from the body! Therefore, treatment with dual or triple combinations and switching antibiotics are necessary to achieve a cure, as well as at least one of the combined antibiotics must be administered parenterally. As far as ciprofloxacin is concerned, it is recommended to administer this agent only by the oral route, in view of the risk of adverse effects. The pathogenetic justification of repeated treatment is that several different subphyla of *Borrelia burgdorferi* sensu lato with diverse antimicrobial-susceptibility profiles may be jointly responsible for the disease process [5]. The need for re-treatment should be established during **follow-up care** [2, 6, 8, 10].

Table 1 – Antibiotic combinations recommended for individualized administration.

Antibiotic	Dosage (mg/day) & route of administration
CIPROFLOXACIN	250 to 500 t.i.d.
A 6-week course in combination with one of the following antibiotics chosen in view of the antibiotic history of the patient:	
DOXYCYCLINE	100 to 150 t.i.d., PO
CLARITHROMYCIN	500 t.i.d., PO
JOSAMYCIN	500 to 1000 t.i.d., PO
DOXYCYCLINE	200 b.i.d., IV
CEFTRIAXON	1-2 x 2000 o.d. or b.i.d., IV
(CLARITHROMYCIN)	500 b.i.d. or t.i.d / 1000 b.i.d., IV

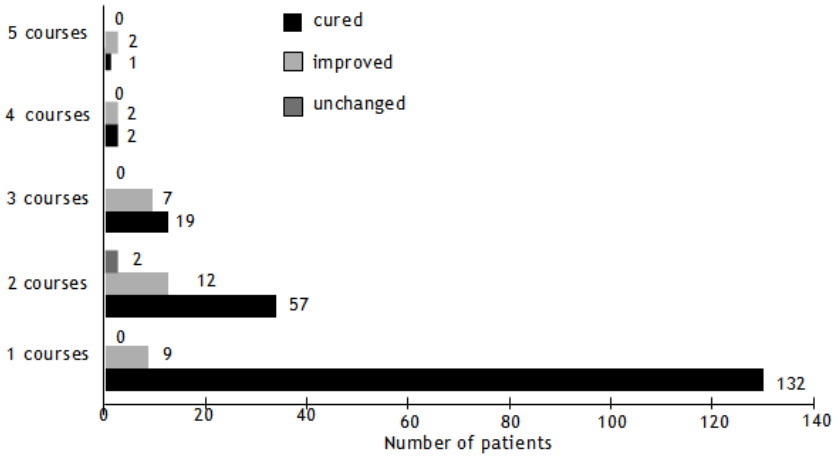

Figure 2. The efficacy of combined antibiotic therapy according to the results of a 5-year follow-up of 250 patients.
The initial treatment determines the number and effectiveness of subsequent courses!

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