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Critical review of studies trying to evaluate the treatment of chronic Lyme disease☆

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Revue critique des études essayant d'évaluer le traitement de la maladie de Lyme chronique

Although antibiotic treatment for Lyme disease is effective in some patients, especially during the early phase of the disease, many patients suffer from chronic disease with persisting and evolving signs and symptoms. The role of persistent microorganisms in the pathophysiology of chronic syndromes following Lyme disease treated according to the current recommendations is still being debated [1–3]. The clinician has no diagnostic test to use in routine practice to check for the persistence of live *Borreliae*. Several publications show contradictory results regarding the treatment of chronic Lyme disease.

Efficacy of prolonged antibiotic treatment for chronic Lyme disease

The efficacy of long-term antibiotic treatment in patients with chronic Lyme disease or chronic syndromes following tick-bites is still controversial [2]. Several open-label studies have shown that a large proportion of patients with chronic Lyme disease improve after prolonged courses of antibiotic treatment [4–6]. For their condition to improve, patients with a long history of the disease required longer antibiotic treatments. Several randomized studies tried to evaluate the efficacy of antibiotic treatment versus placebo in chronic Lyme disease. In one study, no difference was shown [7]. In the two following studies, a significant albeit limited beneficial effect of antibiotic therapy was demonstrated. In the study by Krupp et al., a four-week course of treatment with ceftriaxone improved the fatigue syndrome as reassessed at 6 months, with a significant improvement of 64% in the ceftriaxone group versus 18.5% in the placebo group ($P < 0.001$) [8]. In the study by Fallon et al. that included patients with memory impairment persisting after an initial three-week course of treatment with ceftriaxone, a 10-week long retreatment with ceftriaxone was successful, versus placebo, in improving their cognitive functioning ($P < 0.01$). However, this beneficial effect was transient and the difference between the retreated and the non-retreated groups disappeared after 6 months [9]. This transient effect of antibiotics could be due to bacterial persistence.

B. burgdorferi is highly adaptable and able to persist within tissues

B. burgdorferi has a complex genetic structure. It has more than 132 function genes. In contrast, *Treponema pallidum*, another spirochete, only has 22 function genes. *B. burgdorferi* has one

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linear chromosome and 21 plasmids. *Chlamydophila* only has 7 plasmids. This genetic complexity suggests that *B. burgdorferi* is a highly adaptable organism capable of evading the human immune response. It can do so through different processes such as immunosuppression, antigenic variation, mutation and gene recombination. It can survive extracellularly as well as intracellularly; it releases factors for cell adherence and some studies have shown that it can persist in atypical dormant state forms through cyst formation. The cyclic conversion of cystic forms into free spirochetes releases new *Borreliae* in tissues. Animal models in mice, dogs and monkeys clearly demonstrate that *B. burgdorferi* may persist in tissues even after several months of treatment with antibiotics that are effective in vitro [2,10]. Persistence of *B. burgdorferi* after antibiotic treatment has also been reported in some studies done on humans [11–13]. Dormant persister cells of bacteria from different genera can escape the bactericidal effect of antibiotics and be responsible for latent infections [11–14]. Persisters are quiescent bacterial cells that are able to survive antibiotics or stresses and that are able to resume growth under favorable conditions [15]. Clinicians have no diagnostic tests to check for the persistence of live *Borreliae*. Changes seen in the serologic profile are not contributive. The antibiotic susceptibility profile of the growing forms of *B. burgdorferi* differs from that of the persistent forms of the bacterium [16]. The cystic forms of *B. burgdorferi* are able to escape the antibactericidal effect of antibiotics. Moreover, the persistence of other species of *Borreliae* has not yet been well studied.

Several species of *Borreliae* are pathogenic for humans

Borreliae were initially reported by Charles Nicolle as microbial agents responsible for relapsing fever (*Borrelia recurrentis*). Relapsing fever due to another species of *Borrelia* (*B. crociduroe*) is endemic in some parts of Africa [17]. While Lyme disease is usually described as an infection due to *B. burgdorferi* sensu stricto, to *B. afzelii* and to *B. garinii*, Lyme-like diseases may be due to other species of *Borrelia.* They are rarely considered or tested for, and their antibiotic susceptibility profile is poorly studied [3,14,18]. *Borrelia miyamotoi*, phylogenetically close to relapsing fever borreliae, is now recognized as a cause of Lyme-like disease and relapsing fever in Asia, Europe and North America [14,18]. Another novel isolate of *Borrelia* has been identified by PCR in a post-treatment serum from a patient with neurologic Lyme disease, showing the capacity of this new species to persist despite antibiotic treatment [14]. Few studies have looked at drugs capable of killing persistent *B. burgdorferi* or other species of *Borrelia*.

Activity of drugs against *Borrelia* persisters

Metronidazole and tinidazole, which have a high in vitro activity against *B. burgdorferi*, are also effective against cystic forms of the bacterium [19]. Tigecycline is effective against round-body propagules of *B. burgdorferi* [20]. Some drugs, which are not antibiotics, can play a role against persistent bacteria. It has been suggested in an open-label study that the combination of hydroxychloroquine with antibiotics improves the efficacy of antibiotic treatment against chronic Lyme disease [5]. Hydroxychloroquine and chloroquine are able to enhance the bactericidal activity of antibiotics in the phagolysosome within leucocytes, as shown for *Mycobacterium tuberculosis* or *Coxiella burnetii* [21,22]. Q fever is a good example of the antibacterial use of hydroxychloroquine. When combinations of three antibiotics of different classes were given daily for as long as three years, live forms of *Coxiella burnetii* could still be isolated from the cardiac valves of patients suffering from a chronic form of the disease. The systematic addition of hydroxychloroquine to the antibiotic treatment, consisting of a single antibiotic, doxycycline, for at least 18 months, results in the cure of the majority of chronic Q fever cases. Furthermore, it has been shown that hydroxychloroquine has a direct inhibitory effect against *B. burgdorferi* [23]. In addition to this antibacterial effect, hydroxychloroquine and chloroquine are mainly known as anti-parasitic drugs and their clinical efficacy could be due in part to their activity against parasites responsible for coinfections, such as *Babesiae*. In fact, alternative treatments to antibiotics have rarely been studied [16,24,25]. In these studies, melittin, grapefruit seed extract, clofazimine (already used for leprosy or mycobacteria), bismuth (currently used for *Helicobacter pylori*), amphotericin B (an antifunfal drug), amodiaquin and quinine hydrobromide (effective against *Plasmodium* sp.) should be further studied against persistent forms of *B. burgdorferi*. The study of effective non-antibiotic drugs should be included in the clinical research programs. It could be a partial response to the fear of developing antibiotic resistance when treating cases of chronic Lyme disease.

Role of coinfections in the persistence of signs and symptoms

The limited efficacy of antibiotic treatments observed in some patients could also be due to coinfections with other microorganisms. Acute or chronic syndromes occurring after tick bite may be due, in part or in total, to pathogens other than *Borrelia* sp., some of them tick-transmitted, others transmitted through different mechanisms [3]. Other well-known tick-transmitted infections are human granulocytic anaplasmosis and babesiosis, a frequent parasitic infection of animals. Other bacterial species are also able to persist: *Chlamydophila*, *Mycoplasma*, *Bartonella*, *Coxiella burnetii*, and a new tick-borne bacterial pathogen, *Candidatus Neoehrlichia mikurensis* [26,27]. In addition to bacteria and parasites, viruses such as HHV-6, or fungi such as *Leishmania*, could be involved. Some of these infections may have an impact on the neuropsychiatric status of patients. For example, *Toxoplasma gondii* infection can increase the risk of suicidal behavior [28,29]. As described above, the anti-parasitic

effect of hydroxychloroquine could partly explain its clinical efficacy in some patients through its activity against *Babesiae*. The anti-fungal drug, fluconazole may improve some patients [30]. It is not known if this clinical benefit is due to the activity against a fungal coinfection or if it is due to the presence of receptors to fluconazole on persistent microorganisms.

Critical analysis of studies trying to evaluate the treatment of chronic Lyme disease

Exacerbation of signs and symptoms is a frequent event during antibiotic treatment of Lyme disease. The acute exacerbations at the beginning of treatment, known as the Jarish-Herxheimer reaction, have been well described. Exacerbations occurring during prolonged antibiotic treatment of chronic Lyme disease may occur later in the course of treatment and may have a cyclic course for weeks or months before progressively disappearing (personal clinical observation). The evaluation of antibiotic efficacy, versus placebo, after several weeks of treatment may be biased. The first cause of bias is the cyclic nature of the disease, compounded with the intermittent exacerbations due to antibiotics in the treated group. Some patients in the treated arm who will eventually be cured may experience an exacerbation at the time-point of evaluation. The second bias is when the tool used for evaluation is too general, such as a quality of life score, which does not analyze the different categories of signs and symptoms (general, articular, neurologic, cardiac, etc.). At a given point in time, a certain category of signs or symptoms may have disappeared and improvement may be long term, while another category of signs and symptoms may appear to be transient worsening, leading to the false conclusion of global failure. So, in fact, the two randomized studies, which evaluated specific objective end-points, showed a benefit of antibiotic treatment, whilst the randomized study that used a general quality of life score did not. The design of future randomized studies should take into account these potential pitfalls.

Conclusion

Fundamental and clinical research is needed to move forward in the management of patients suffering from chronic Lyme disease or associated diseases. New PCR methods and new genomic techniques, such as high throughput sequencing, should be used to identify the microorganisms that could be involved in a particular patient [14]. New strategies should be designed in order to determine the best treatments against *Borrelia* sp. and the possible coinfections. The addition of a maintenance phase treatment to the induction phase treatment is probably needed in some patients. As well as drugs that are well-known to be effective against bacteria in their growth phase, other drugs, which can be effective against persistent bacteria, should be evaluated for their efficacy in the maintenance phase of treatment.

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