Editorial

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Advances in the treatment and prevention of Lyme borreliosis

Lyme borreliosis is the most clinically complex of the spirochetal infections for a variety of reasons. First, is the potential for manifestations involving multiple systems, particularly the skin, joints, nervous system, and heart. Second, there are both early and late manifestations, as well as intervening periods of clinical latency in which infected patients are asymptomatic [1–3].

These general characteristics, however, do not distinguish Lyme borreliosis from another important spirochetal infection, syphilis. The greater clinical complexity associated with Lyme borreliosis becomes apparent only after more thorough analysis. The clinical manifestations of syphilis in Europe and North America, and approaches to diagnosis and prevention are presumed to be identical. This is not the situation for Lyme borreliosis. Differences arise because of the greater diversity of species of Lyme borrelia in Europe compared to North America [1, 2, 4] and because the only borrelial species known to cause infection in North America (*Borrelia burgdorferi* [also referred to as *B. burgdorferi* sensu stricto]) causes less than 30% of infections in Europe [5]; the other borrelial pathogens in Europe include *B. afzelii* and *B. garinii* (Table 1). Certain clinical manifestations are closely associated with infection due to a particular species. As a consequence, some dermatological conditions, such as acrodermatitis chronica atrophicans and borrelial lymphocytoma, are nearly exclusively found in Europe [1, 2], whereas other manifestations, such as erythema migrans or neurological symptoms and signs, occur in both locations.

Differences also are apparent in regard to diagnostic testing between Lyme borreliosis in North America and Europe [6]. Both the greater diversity of species causing infection, and the lower frequency of seropositivity in European patients with erythema migrans caused by *B. afzelii* compared to *B. burgdorferi* [7, 8], makes serologic diagnosis much more challenging in Europe.

The papers on Lyme borreliosis in this issue of Wiener klinische Wochenschrift discuss important aspects of prevention and treatment of Lyme borreliosis based on studies principally conducted in North America [9, 10]. Avoiding tick bites is the centerpiece of prevention. While general approaches to prevention should largely be the same in Europe and in North America, differences in the infecting borrelia species, as well as in the vector ticks, do appear to impact on prevention strategies. For example, the monovalent recombinant outer surface protein A (OspA) vaccine preparation found to be approximately 80% effective for prevention of definite cases of Lyme borreliosis in North America [11], would be expected to be less successful in Europe, given the much greater diversity of the OspA molecule on the species of Lyme borrelia there [12, 13]. Unfortunately, marketing of the OspA vaccine preparation was discontinued due to poor sales, although a similar preparation remains available for use in dogs. An experimental OspA vaccine preparation is being evaluated for immunization of field mice and early studies have shown promising results [14]; a noteworthy feature of certain OspA preparations is their effectiveness as an immunogen for mice when ingested [15, 16].

Another interesting difference between continents is the much shorter time from tick bite to transmission of Lyme borrelia in experimental studies of animals, by the European tick *Ixodes ricinus* [17], compared with the North American ticks *I. scapularis* [18–20] and *I. pacificus* [21]. Clinical studies have suggested that there is a substantial delay in transmission of *B. burgdorferi* to humans after attachment of *I. scapularis* ticks [22, 23], but similar data are lacking for *I. ricinus* tick bites. Pending such studies, Europeans may be well advised to check for and remove attached *I. ricinus* ticks within 6 hours of exposure.

Single-dose doxycycline (200 mg) was found to be 87% effective for prevention of Lyme borreliosis in North America after an *I. scapularis* tick bite [23]; and longer courses of antibiotics (10 days) were 100% effective [24–26]. Korenberg et al reported on the use of doxycycline for prevention of Lyme borreliosis in persons bitten in Russia by *I. persulcatus* ticks shown by microscopy to contain spirochetes [27]. None of the 120 subjects who received a 3 day course of doxycycline and none of an additional 141 subjects who received a 5 day course of doxycycline developed erythema migrans at the tick bite site, the only certain criterion of failure of antibiotic prophylaxis. Overall, 3 (1.1%) of the 261 doxycycline treated subjects developed any evidence of Lyme borreliosis compared to 12 (12.4%) of 97 persons who received no antibiotic therapy ($p < 0.001$). However, given anecdotal reports of the failure of antibiotic prophylaxis of *I. ricinus* tick bites in Slovenia [28], controlled studies should be performed in Europe before extrapolating from results observed in either North America or Russia.

So much similarity in antimicrobial susceptibility exists among isolates of different species of Lyme borrelia (at least in the limited testing done to date) [29, 30], that there is little reason to expect differences between North America and Europe in either the efficacy of specific antibiotics or in duration of therapy. In both locations,

Table 1. Comparison of selected aspects of the treatment and prevention of Lyme borreliosis in North America and Europe

Feature	North America	Europe	Comment
Principal vector Principal etiologic agents	*Ixodes scapularis* *Borrelia burgdorferi*	*Ixodes ricinus* *Borrelia afzelii* *Borrelia garinii* *Borrelia burgdorferi*	In Europe, greater diversity of clinical manifestations and more obstacles to serodiagnosis, because infection may be due to at least 3 different species of Lyme borrelia
Transmission of Lyme borrelia to experimental animals by vector	0% within 24 hours (ref. [20])	50% within 24 hours (ref. [17])	To prevent transmission of Lyme borrelia to humans, *I. ricinus* ticks should probably be removed within 6 hours of attachment, whereas removing *I. scapularis* ticks within 24 hours should be adequate
Chemoprophylaxis	Single-dose doxycycline 87% effective	No controlled studies have been reported on the use of antibiotic prophylaxis for *I. ricinus* tick bites	Anecdotal failures of antibiotic prophylaxis of *I. ricinus* tick bites are reported (ref. [28])
Immunoprophylaxis	A monovalent OspA vaccine preparation was ~80% effective, but is currently not marketed	Not available	A multivalent vaccine would be preferable in Europe, due to the greater antigenic diversity of the etiologic agents
First-line treatment	Doxycycline Amoxicillin Cefuroxime axetil Ceftriaxone	Doxycycline Amoxicillin Phenoxymethyl penicillin Cefuroxime axetil Ceftriaxone	Although more study is needed, type of antibiotic and duration of therapy is expected to be similar between North America and Europe

doxycycline or amoxicillin, certain cephalosporins such as cefuroxime axetil, cefotaxime or ceftriaxone, and certain macrolides such as azithromycin are highly efficacious [31–35].

Increasing attention is being paid to reducing duration of antibiotic therapy in many infectious diseases [36–38]. Shorter courses of antibiotic treatment are likely to be safer, less costly, more convenient for the patient, and less likely to promote the emergence of resistance in fecal flora. Prolonged administration of a single antibiotic can lead to the selection of intestinal bacteria, not just resistant to the antibiotic used, but to multiple structurally unrelated antimicrobials (36,39,40). A recent double-blind, randomized, controlled trial from North America showed that 10 days of doxycycline had similar efficacy to 20 days of treatment in patients with early Lyme disease who had erythema migrans [41]. Of note, although many patients remained symptomatic at the end of the course of antibiotic therapy, they continued to improve after treatment and did so at the same rate regardless of whether they were treated for 10 or 20 days with doxycycline therapy. The possibility that antibiotic therapy might be shortened even further is suggested by a study of patients with erythema migrans reported from Germany [42].

In this issue of Wiener klinische Wochenschrift, Dattwyler and colleagues [10] report on a non-blinded, randomized multi-center trial in which 14 versus 28 days of ceftriaxone were compared in 143 patients from North America with late stage Lyme borreliosis, manifested predominantly as Lyme arthritis. At time of last evaluation up to one year after completion of antibiotic treatment, clinical cure rates were 76% in the 14-day group and 70% in the 28-day group ($p = 0.50$). To be considered a clinical cure all signs and symptoms had to have resolved completely. At time of last evaluation, there were 5 patients who had no change in their symptoms in the 14-day treatment group compared to none in the 28-day treatment group ($p = 0.07$). Use of a variable time point for the primary outcome measure, however, may have served to exaggerate rather small differences. At the 3, 6 or 12 month specific time points of evaluation, there were 1–2 non-responders in the 14-day group versus 0-1 non-responders in the 28-day group. Whether there is a subgroup of patients who might benefit from a treatment course extended to 28 days, could not be determined from this study. In favor of shorter treatment courses, a significantly greater proportion of patients assigned to the 28-day treatment arm had to have their therapy discontinued prematurely due to adverse events ($p < 0.02$). Several patients in this study (including both treatment groups) developed well recognized potentially life-threatening complications associated with ceftriaxone therapy [43,

44], including three cases of diarrhea due to *Clostridium difficile*, one case of cholelithiasis, and one case of granulocytopenia.

Analogous to the findings in the controlled treatment trial of patients with early Lyme disease (discussed above), resolution of symptoms in the Dattwyler study also continued after antibiotic therapy was completed. Clinical cure rates were greater at 12 months than at 3 months in both the 14-day and 28-day treatment groups.

Lyme borreliosis is a complex spirochetal infection. Despite the availability of diverse strategies for prevention as described in this issue of Wiener Klinische Wochenschrift [9], Lyme borreliosis remains the most common tick-borne infection in both North America and Europe [45, 46], and the incidence appears to be rising rather than falling in the United States and some European countries [47, 48]. Lyme borreliosis, like other spirochetal infections, is antibiotic responsive. In both early and late stages of infection in North America, it is, however, increasingly evident that resolution of symptoms is generally not hastened by extending antibiotic therapy beyond 14 days. Patients should be forewarned that they may not be asymptomatic at time of completion of antibiotic therapy and reassured that in the vast majority of instances their symptoms will continue to improve steadily over the course of time.

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