Lyme arthritis and post-Lyme disease syndrome

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In the United States, intermittent or chronic mono- or oligoarthritis, particularly affecting the knee, is the most common manifestation of late Lyme disease (LD). Lyme arthritis (LA) can usually be prevented by early treatment of acute LD. However, the erythema migrans rash may go undetected in children and in the dark skin of African Americans, leading to delayed treatment and a relatively increased incidence in LA. Virtually all untreated patients with LA have high levels of serum immunoglobulin G antibodies, and sometimes low levels of immunoglobulin M antibodies, to *Borrelia burgdorferi* (Bb) by ELISA and Western blot. These responses may persist for many years after antibiotic treatment, and therefore, serologic results do not accurately distinguish between active or past infection. Most patients with LA respond well to standard courses of antibiotic treatment, but a small percentage have persistent knee synovitis, in some cases possibly related to the triggering of intrasynovial autoimmunity. Other patients develop a syndrome of diffuse arthralgia, myalgia, fatigue, and subjective cognitive difficulty during or soon after LD, which persists despite antibiotic treatment. Patients with this post-treatment, post-LD syndrome were recently studied in a placebo-controlled double-blind antibiotic trial. There was no evidence of Borrelial infection in these patients by culture or detection of Bb DNA in blood or spinal fluid. Furthermore, there was no difference in responsiveness of these patients to a 3-month course of antibiotic compared with placebo treatment. Thus, LA caused by active Bb infection, post-treatment LA with persistent knee synovitis and post-LD syndrome are distinct and distinguishable clinical entities. Curr Opin Rheumatol 2002, 14:383–387

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Abbreviations

Bb	*Borrelia burgdorferi*
EM	erythema migrans
IgG	immunoglobulin G
IgM	immunoglobulin M
LA	Lyme arthritis
LD	Lyme disease
OspA	outer surface protein A
PCR	polymerase chain reaction
ReA	reactive arthritis
SF	synovial fluid

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Lyme arthritis

Clinical description and epidemiology

In the United States, arthritis is the most common manifestation of late Lyme disease (LD). A recent comprehensive review of LD described the clinical features, diagnosis, and treatment of Lyme arthritis (LA) [1••]. Arthritis is observed in about 60% of untreated or incompletely treated patients a few months after the onset of disease. Initially this is an intermittent asymmetric mono- or oligoarthritis of large joints with a predilection for the knee joint. Recurrent inflammation may continue for weeks to months. If left untreated, many of these patients eventually develop an acute or subacute arthritis of one or both knee joints resembling, in an adult, septic arthritis, crystalline-induced arthritis, or reactive arthritis. The affected joint may have a large effusion and the synovial fluid (SF) is inflammatory but nonpurulent. Virtually all untreated patients with LA have serum immunoglobulin G (IgG) antibodies to *Borrelia burgdorferi* (Bb) by Western blotting. Culture of synovial fluid does not reveal Bb, but Bb DNA can be demonstrated by polymerase chain reaction (PCR) in a majority of untreated patients with LA [2]. Both oral and parenteral regimens have been used successfully to treat LA [3]. Oral doxycycline 100 mg twice daily or amoxicillin 500 mg three times daily for 28 days can be used in patients without evidence of concomitant neurologic disease. A 2- to 4-week course of intravenous ceftriaxone 2 g/d may also be used. Oral regimens are less expensive and easier to administer and to tolerate than parenteral treatment. Despite appropriate antibiotic therapy for LA, a small percentage of patients develop continuous chronic arthritis for many months to years.

Early antibiotic therapy of LD can prevent the development of late features such as LA. Thus detection of erythema migrans (EM), the cardinal clinical sign of early LD, is critical to early diagnosis. However, EM can be missed in individuals with colored skin. Fix *et al.* [4•] analyzed the Maryland Lyme Disease Registry from 1993 to 1996. Among all the manifestations of LD, the greatest difference between Caucasians (C) and African Americans (AA) was in the reported incidence rate (IR) of EM, both across the state (5.7 cases per 100,000 population per year *vs.* 0.3, an incidence rate ratio (IRR) of 17.7) and in endemic areas, IR (C) 28.0 *versus* IR (AA) 4.9, IRR 5.7. In contrast, the frequency of LA in an endemic area revealed an IR (C) of 17.4 and IR (AA) of 18.5 with an IRR of 0.9. The authors concluded that the relative increase of LA in AA was related to the

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decreased recognition of EM, resulting in delayed treatment of LD.

Approximately 90% of children in endemic areas present with EM, which allows diagnosis and treatment in an early stage with excellent prognosis. Children, however, may be more likely than adults to have an unrecognized or undiagnosed single EM lesion [5]. Thus the diagnosis of LD may be delayed with resulting progression to late stages, especially arthritis. Bentas *et al.* [6•] followed prospectively a group of 55 children and adolescents with LA. Ten (18%) children had LA from the outset and 17 (31%) progressed to chronic arthritis. Overall, LA was more benign in younger children and more chronic in those older than 10 years of age. Girls were more likely to develop chronic LA. Intraarticular steroids given before initiation of antibacterial treatment increased the risk of antibiotic failure. These data demonstrate the importance of host-related, and possibly iatrogenic factors in the clinical course of LA.

Lyme vaccination and arthritis

An outer surface protein A (OspA)-based vaccine has been shown to be safe and effective in preventing LD in two large, randomized, placebo-controlled studies in adults [7,8]. Recently, similar results were reported in children by Sikand *et al.* [9••]. In that trial, 3,063 children aged 4 to 18 years received an OspA-based vaccine against LD. Children developed higher IgG titers of anti-OspA antibody than reported in adults; however, no child developed persistent vaccine-related inflammatory arthritis.

Shadomy *et al.* [10] conducted a study using the Vaccine Adverse Event Reporting System (VAERS) reports. Based on the distribution of approximately 1.4 million vaccine doses, 415 patients with arthralgia or possible arthritis were reported. Forty-nine telephone interviews were completed and 31 medical records reviewed. Fourteen (28.6%) of the 49 interviews were classified as "physician-diagnosed arthritis." In 7 of 14 cases, the authors found another explanation for the arthritis. The major limitation of this study is that the patients were not examined and that any direct link between vaccination and arthritis was not proven. Even so, the overall incidence of "possible arthritis" following vaccination was very low.

However, despite these large clinical studies, there is a theoretical and experimental reason to remain cautious about the arthritogenic risk of an OspA-based Lyme vaccine. Patients with LA often have high titers of antibodies to OspA [1••]. A study by Croke *et al.* [11] provided evidence of experimental induction of arthritis by OspA. Hamsters vaccinated with increasing doses of recombinant OspA in aluminum hydroxide were subsequently challenged with Bb sensu stricto. Hind paw swelling was detected in all animals vaccinated with 30 and 60 μg and in half of animals vaccinated with 120 μg of rOspA. Lin *et al.* [12] demonstrated that Bb OspA is capable of inducing dose-related release of matrix metalloproteinases, MMP-1 and MMP-3, from chondrocytes in cell culture. Furthermore, MMP-3 has the ability to activate other MMPs [13]. Thus, theoretically OspA could induce or potentiate synovitis.

Rose *et al.* [14•] reported four cases of arthritis after OspA vaccination in humans. Two cases of acute transient symmetrical polyarthritis of small joints occurred in adults after the inoculation of the second dose of vaccine; both patients fully recovered without antibiotics. Two other cases involved children. A 9 year-old HLA-DR4 positive boy developed severe polyarthritis after the third dose of vaccine. Anti-Bb IgG Western blot showed 15 reactive bands. He became asymptomatic after a 28-day course of amoxicillin. The authors postulated that an extensive immunologic reaction mounted by the patient could have occurred as a result of vaccination of an already infected child. Another teenage boy had persistent oligoarthritis after he had received 3 doses of vaccine. Antibody response to Bb by Western blot showed two IgM and four IgG bands, including a 31kDa region (anti-OspA) band. These data were interpreted as a probable vaccine reaction. Thus, there is a possibility that an OspA-based vaccine may rarely induce inflammatory arthritis.

In February 2002, GlaxoSmithKline discontinued production and distribution of the only approved OspA-based vaccine. Thus there is currently no vaccine available for the prevention of LD.

Attenuation of Lyme arthritis in pregnancy

Little is known about the effect of pregnancy on the clinical progression of Lyme arthritis. Pregnancy alters cytokine levels to protect the fetus from Th1 cell-mediated immunity of the mother. Moro *et al.* [15•] studied the progression of LA in pregnant mice infected with Bb. While nonpregnant mice consistently developed severe LA, pregnant mice showed marked reduction in arthritis severity. Higher levels of Th2 cytokine, IL-4, was found in pregnant compared with nonpregnant mice. A slight reduction in T cell production of the Th1 cytokine INF-γ was also noted in a group of pregnant mice. This shifting of immune responses toward humoral immunity and blunting of cell-mediated immunity could explain the amelioration of experimental arthritis. This effect was reproduced in nonpregnant animals by treatment with progesterone. In contrast, neutralization of IL-4 in progesterone-implanted mice resulted in severe arthritis. To date, this phenomenon has not been reported in humans.

Long-term serologic status after Lyme arthritis

Kalish *et al.* [16••] examined the serologic status of 79 patients who had LD 10 to 20 years previously, who had no evidence of active LD at the time of follow up, and

who had serum available from their original illness for paired antibody testing with follow-up specimens. Of these patients, 39 had LA with their original illness. In their initial serum samples, 15 (38%) LA patients had an IgM response and all had an IgG response to Bb. In the follow-up samples, 6 patients (15%) continued to have IgM antibodies and 24 (62%) IgG antibodies. Twenty-six of the 39 LA patients (67%) had either IgM or IgG antibodies to Bb 10 to 20 years after active LA. This observation demonstrates that serologic test results alone cannot distinguish between active or past infection. It reinforces the principle that serologic testing should be used to support a diagnosis of LD in conjunction with current clinical symptoms.

Chronic Lyme arthritis and reactive arthritis

There are many potential causes of persistent LA after standard courses of antibiotic therapy. Some patients who continue to have arthritis after antibacterial treatment eventually improve; some are probably slow responders, whereas others may have suffered some mechanical damage to the joint structures from the inflammation and large effusion. This is supported by a long-term cohort follow-up study by Kalish *et al.* [17•]. They reported on the current status of 84 patients 10 to 20 years after the original diagnosis of LD, and compared them with 30 non-LD controls. Of the 42 patients with prior LA, 16 (38%) continued to have episodic or chronic knee pain. Some of the patients had limitation of motion and small effusions, suggestive of degenerative arthritis. This was not seen in the comparison patients who never had LA. Rarely, treatment-resistant chronic arthritis may be caused by persistent synovial infection, supported by detection Bb DNA in synovial fluid or synovium [2,18]. However, Priem *et al.* [19] demonstrated that Bb DNA could be detected by PCR in a human synovial tissue culture model after antibiotic treatment despite negative cultures. This raises the possibility that in some patients, detection of Bb DNA by PCR in SF or synovium could represent delayed clearance of already killed microorganisms, rather than persistent infection. A recent study of six patients with infectious arthritis (not LA) showed that PCR positivity can persist in culture negative synovial fluid or synovial tissue for 1 to 2 weeks, but rarely longer [20]. There are studies supportive of an autoimmune chronic synovitis following LA in some patients, including a distinct subgroup of patients with an increased frequency of HLA-DR4, especially HLA-DRB1*0401 and related alleles, the same alleles that are associated with severity in rheumatoid arthritis [21]. Steere *et al.* [22•] proposed a model of molecular mimicry explaining these cases of persistent treatment-resistant arthritis. One immunodominant epitope of OspA presented by the HLA-DRB1*0401 or related alleles has sequence homology with human leukocyte function associated antigen–1 (hLFA-1), a molecule expressed on T cells in inflamed synovium. This could lead to immunologic cross reactivity and result in persistent inflammatory synovitis even in the absence of viable Bb.

It remains unclear whether some patients with LA actually have a form of reactive arthritis (ReA) induced by Bb. [23–25]. There are many microbes able to trigger ReA, and in one study Bb was implicated as a potential cause in the genetically susceptible HLA-B27-positive host [23]. This concept has been further expanded by Schnarr *et al.* [26•]. They prospectively studied a group of 52 patients with undifferentiated mono- or oligoarthritis. Nine (17%) patients had *Chalmydia trachomatic* (Ct) DNA and 6 (12%) patients had Bb OspA DNA in the SF by a nested PCR technique. None of the patients fulfilled the Centers for Disease Control and Prevention criteria for LD and none were seropositive for LD (synovial fluid antibody levels were not measured). HLA status was not reported in these patients. To further complicate this picture, the same investigators in another article described 6 patients with coexistence of both Ct and Bb DNA in SF [27]. Only two of these six patients were HLA-B27 positive. These findings are difficult to explain. It is not known whether these patients were treated with antibiotics, or whether they had a self-limited or chronic clinical course. It is possible that the PCR results in this study are incorrect because of technical problems, because it is well known that PCR may be subject to false positive results [28•,29]. Even if the validity of PCR-based tests is proven to be correct, the significance of these findings in human arthritis is unclear. What does detection of Bb DNA prove in the face of negative Lyme serology? As pointed out in an editorial by Sigal [30•] and the experiments of Priem *et al.* [19], the presence of a detectable PCR product does not necessarily indicate viable organisms. On the other hand, could these results point to a "reactive" or immunologic nature of the arthritis? It is important that these findings be confirmed at other institutions.

The role of coinfection in Lyme arthritis

Ixodes scapularis is the vector for both Bb and the organism causing human granulocytic ehrlichiosis (HGE). Dual infection in humans can occur in highly endemic areas [31]. The role of coinfection with Bb and HGE in experimental LA was studied by Thomas *et al.* [32]. They used C3H/He mice known to develop severe arthritis of the tibiotarsal joints after intra-articular injection with Bb. At the peak phase, two weeks after inoculation, the joints of coinfected mice had approximately tenfold more Bb DNA than the joints of mice infected with only Bb. Histopathologic examination showed more severe arthritis in coinfected animals. Although LA is generally associated with a Th1 response, at 2 weeks postinfection, sera of coinfected mice had features of a Th2 response with diminished levels of IL-12, TNF-α, and INF-γ, and increased IL-6 levels. The data suggest that other factors such as bacterial burden, and particu-

larly coinfection, may be relatively independent driving forces in LA. These studies have yet to prove relevant to the human disease.

Post-Lyme disease syndrome

Although the long-term prognosis of treated LD is excellent, some patients have arthralgia, myalgia, and fatigue, during or soon after LD, despite adequate courses of antibiotics [33]. Other symptoms are common, including memory and concentration difficulties, neuropathic pains, headache, and unrefreshed sleep [34]. This condition is often called post-LD syndrome, chronic LD, or LD-induced fibromyalgia (FM). The actual frequency of this condition after LD is unclear. Long-term follow-up studies on LD patients have shown a wide variation in the frequency of persistent symptoms, from common [33,35] to unusual [36]. Kalish *et al.* [17] found that the subgroup of patients with acute neurologic involvement initially, such as those with facial palsy that was often accompanied by more widespread involvement of the nervous system, were more likely than the other groups (EM or LA) to develop chronic symptoms of memory difficulty. This suggests that clinically obvious or subclinical neurologic involvement may cause structural damage or functional impairment that contributes to this syndrome. However, other studies have not shown this association with earlier neurologic disease [33,37]. In the Kalish study, patients who developed persistent symptoms were more likely to have been untreated during their initial illness. This is in keeping with some other studies which suggest that delay in initiating treatment for acute LD, even without clinical neurologic involvement, was more likely to result in post-LD syndrome [33,35]. In none of these studies did current serologic status correlate with persistent symptoms [17,33,35].

Although these patients have significant somatic complaints and functional disability, they lack objective findings of an inflammatory condition. Virtually all patients with post-LD syndrome complain of problems with memory and concentration. However, demonstrable abnormalities on neurocognitive testing are not universally present [17,35]. A recent investigation of cognitive defects in 20 children with chronic LD compared with 20 age and gender-matched controls revealed significantly more cognitive and psychiatric disturbances in the LD group, including anxiety and depression [38•]. This resulted in psychosocial and academic impairment. However, in some of these children there was a long delay in diagnosis (mean time to diagnosis was 47.28 weeks) and consequently a delay in treatment. Thus, some of these children may have had true neurologic LD. Another problem with this study is that it is cross-sectional rather than longitudinal. Therefore, assessment of premorbid cognitive function was only indirectly estimated using prior school records.

The pathogenesis of this chronic post-treatment symptomatic state is unclear. Patients may feel better during antibiotic therapy, but the effect is not durable and relapse is common when antibiotics are discontinued. The symptoms wax and wane but the overall course is chronic. Controversy has raged as to whether chronic relatively resistant infection plays a role, and hence whether chronic antibiotic therapy is warranted. One study suggested that Bb DNA can be found in the muscles of some of these patients [39]. Furthermore, some physicians have claimed that chronic antibiotic therapy is ameliorative [40]. However, an important controlled study on 129 post-LD syndrome patients by Klempner *et al.* [41••] failed to document the presence of Bb in the plasma or spinal fluid of these patients by culture or PCR. In addition, there was no difference in responsiveness to a 3-month course of antibiotics (1 month intravenous ceftriaxone followed by 2 months oral doxycycline) compared with 3 months of placebo treatment. About one-third of patients improved, one-third stayed the same, and one-third worsened. This study suggests that chronic infection is not the cause of post-LD syndrome, that the condition spontaneously waxes and wanes, and that prolonged antibiotic treatment does not result in long-term symptom remission.

Thus LA, which follows untreated or incompletely treated early LD, is clearly infectious and must be distinguished from post-treatment LA, which is usually noninfectious and may have an autoimmune basis, and post-LD syndrome, which is noninfectious and of unknown cause.

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