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Lyme Arthritis

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INTRODUCTION

Epidemiology

Lyme arthritis was originally recognized because of an outbreak of monoarticular and oligoarticular arthritis in children in Lyme, Connecticut in the 1970s.[1] It then became apparent that Lyme disease was a complex multisystem illness affecting primarily the skin, nervous system, heart or joints.[2] Prior to the use of antibiotic therapy for treatment of the disease, about 60% of untreated patients developed Lyme arthritis, a late disease manifestation.[3] In recent years, 30,000-40,000 cases of Lyme disease have been reported annually to the Centers for Disease Control and Prevention (CDC), and in a third of reported cases, arthritis was a manifestation of the disease.[4] However, CDC estimates suggest the actual number of patients diagnosed with Lyme disease annually may be 10-fold higher.[5] There is a male predominance (60% cases) among reported Lyme arthritis cases.[4] Although Lyme disease may affect individuals of any age, there is a bimodal age distribution with middle-aged adults and children being most affected; 35% of reported Lyme arthritis cases between 2008-2015 were in the 10-14 year old age group.[4]

The infection is transmitted primarily by nymphal *Ixodes scapularis* ticks, which quest in the late spring and early summer.[6] However, Lyme arthritis can present at any time of the year. The majority of cases occur in the Northeastern, Mid-Atlantic and upper-Midwestern areas of the United States.[4]

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In the United States, *Borrelia burgdorferi* is the sole cause of Lyme disease, and arthritis is the primary disseminated disease manifestation. In contrast, in Europe where *B. afzelii* and *B. garinii* are the major agents of Lyme borreliosis, acrodermatitis and neuroborreliosis, respectively, are more frequent manifestations than arthritis.[7] Subtypes of *B. burgdorferi* also differ in pathogenicity.[8,9] OspC type A (RST1) strains, which account for 30-50% of the infection in the northeastern US,[8,9] but only 3% in mid-Western states,[10] are particularly virulent and arthritogenic. These strains are thought to have played an important role in the emergence of the Lyme disease epidemic in the northeastern U.S. in the late 20th century.[11]

Pathogenesis

B. burgdorferi often disseminates to joints, tendons or bursae early in the infection.[6] Although this event may be asymptomatic, transient or migratory arthralgias may occur at that time. Lyme arthritis, a late disease manifestation, usually occurs months later. Why there is a delay in onset of arthritis following the initial infection is unclear. However, one explanation may be that the spirochete initially evades immune clearance by residing in relatively avascular structures such as tendons and later invades synovial tissue.[12] Lyme arthritis is accompanied by intense innate and adaptive immune responses, particularly Th1 responses in synovial mononuclear cells to *B. burgdorferi* antigens, producing large amounts of IFN-γ.[13] The adaptive immune response leads to the production of specific antibodies, which opsonize the organism, facilitating phagocytosis and effective spirochetal killing.

With appropriate oral and, if necessary, IV antibiotic therapy, spirochetes are eradicated, and joint inflammation resolves in the great majority of patients. However, in a small percentage of patients (<10%), synovial inflammation persists for months or several years despite receiving oral and intravenous antibiotic therapy for 2 or 3 months, called post-infectious or post-antibiotic arthritis (previously antibiotic-refractory arthritis).[14] Steroid use prior to antibiotic treatment may be associated with a refractory outcome.[14,15] In children, older age, longer duration of arthritis prior to diagnosis, and poor initial response to antibiotics are risk factors for this outcome.[16]

The synovial lesion in patients with post-infectious Lyme arthritis (LA) is similar to that of other chronic inflammatory arthritides, such as rheumatoid arthritis, with marked synovial fibroblast proliferation, fibrosis, and infiltration of mononuclear cells (Figure 1). However, there is more evidence of vascular damage in post-infectious LA, with obliterative microvascular lesions seen in approximately 50% of patients, which is a unique feature of LA synovia.[17] A combination of pathogen and host-associated factors (Table 1) contribute to post-infectious LA.[18]

Post-antibiotic LA is associated with infection with highly inflammatory strains of *B. burgdorferi* (RST 1 strains) commonly found in the northeastern United States. However, persistent infection in the post-antibiotic-period does not appear to play role in this outcome. PCR testing of synovial fluid for *B. burgdorferi* DNA, which is often positive prior to treatment, is usually negative by the conclusion of antibiotic treatment, and both culture and PCR testing of synovial tissue have been uniformly negative from synovectomy specimens obtained months to years after antibiotic therapy. [19] Although active infection has resolved, spirochetal remnants may play a role in driving continued inflammation in the

post-infectious period. In MyD88 −/− mice, which have high pathogen loads, spirochetal antigens are retained on cartilage surfaces.[20] *B. burgdorferi* peptidoglycan, a cell wall component which is difficult to clear, has been found in synovial fluid of LA patients and has been shown to trigger arthritis in BALB/c mice.[21]

However, the critical factor in post-infectious LA seem to be an excessive, maladaptive host inflammatory response during the infection, and failure to down-regulate inflammatory responses appropriately after spirochetal killing.[22] The excessive proinflammatory response prevents tissue repair and return to homeostasis following spirochetal killing and results in vascular damage, autoimmune responses, cell-mediated cytotoxicity, and fibrosis. A hallmark feature of post-infectious LA is exceptionally elevated IFN-γ levels which persist in the post-infectious period, accompanied by inadequate levels of the anti-inflammatory cytokine IL-10.[18] Patients with a TLR1 polymorphism (1805GG), which is found in half of the European Caucasian population, are at risk for excessively elevated IFN-γ levels in joints when infected with *B. burgdorferi* RST1 strains.[23] Similarly, specific HLA-DR alleles, such as DRB1:0401 that bind an epitope of *B. burgdorferi* outer-surface protein A (OspA), may also predispose to elevated IFN-γ levels.[24] Further, immune dysregulation may result from an imbalance in Th-1 effector-T regulatory cells, as some cells which are ordinarily regulatory T cells secrete large amounts of IFN-γ. [25,26] In addition, patients with post-infectious LA may have T and B cell responses to Lyme-disease-associated autoantibodies to vascular antigens, such as endothelial cell growth factor, apolipoprotein B-100, or annexin A2 or to matrix metalloproteinase-10, which may further contribute to pathology.[27-29] IgG4 Lyme disease autoantibody titers correlate with magnitude of obliterative microvascular lesions and fibrosis in synovial tissue.[30]

Despite heightened immune reactivity, post-infectious arthritis eventually resolves. Thus, it seems that spirochetal killing, either by the immune system or with the assistance of antibiotic therapy, removes the innate immune “danger” signals. Without these signals, the adaptive immune response to autoantigens eventually regains homeostasis, and the arthritis resolves. This process may be facilitated by therapy with disease modifying anti-rheumatic drugs (DMARDs).

CLINICAL PRESENTATION

During the 1970s before the cause of the disease was known, the natural history of Lyme arthritis was elucidated in a study of 55 non-antibiotic-treated patients who were followed prospectively from onset of erythema migrans (EM), the initial skin lesion, through the period of arthritis.[3] Clinical features of the infection in these patients included the following:

- Arthritis began from 4 days to 2 years (mean, 6 months) after the EM skin lesion.
- Patients had intermittent or persistent attacks of joint swelling and pain, primarily in one or a few large joints, especially the knee, during a period of several years.[3] However, particularly in earlier episodes, other large or small joints, the temporomandibular joint, or periarticular sites (bursa, tendons) were sometimes affected.
- Generally fewer than 5 joints were affected at one time.

- Knee joints were often very swollen, but not particularly painful, and ruptured Baker's cysts were common.
- By the time arthritis was present, systemic manifestations (fever or other constitutional symptoms) were uncommon.

In present times, early Lyme disease is often recognized and treated with antibiotics, preventing the development of arthritis. Therefore, LA now occurs primarily in patients with asymptomatic early infection in whom arthritis is the presenting manifestation of the disease. Thus, the diagnosis should be considered in patients from endemic areas presenting with a monoarticular or oligoarticular arthritis, whether or not there is an history of an antecedent tick bite, flu-like illness, or EM rash.

Patients with Lyme arthritis typically lack fever or prominent systemic symptoms. Since acute neurologic involvement, meningitis, facial palsy, radiculoneuropathy or carditis occur with early disseminated infection, they are rarely seen concurrently in LA patients. However, in rare cases, patients with Lyme arthritis may have a concurrent sensory polyneuropathy or radiculoneuropathy.

Differential Diagnosis

In addition to serologic testing, clinical features may distinguish Lyme arthritis from other entities (Table 2). A common concern is mechanical injury in an active individual, and therefore, orthopedists are often the first specialist to see LA patients. However, the clinical picture of Lyme arthritis is most like reactive arthritis in adults or oligoarticular juvenile idiopathic arthritis in children, and serologic testing is essential to distinguish LA from these entities. Children may have a more acute presentation, with higher synovial WBC counts, which may suggest a diagnosis of acute septic arthritis.[31-33] However, Lyme arthritis typically causes only minimal-to-moderate pain with passive range of motion, and involvement of more than one joint (currently or by history) may help to distinguish Lyme arthritis from septic bacterial arthritis.[31-33] Lyme arthritis rarely, if ever, causes chronic, symmetrical polyarthritis, which helps to distinguish Lyme arthritis from rheumatoid arthritis and lupus. Fibromyalgia is sometimes misdiagnosed as "chronic" Lyme disease, but patients with fibromyalgia generally have diffuse pain, and they lack objective evidence of joint inflammation. However, a subset of patients, usually following early Lyme disease, may experience persistent pain, fatigue and neurocognitive symptoms after appropriate antibiotic treatment, known as post-treatment Lyme disease syndrome (PTLDS).[34] The clinical picture in these patients is like that seen in fibromyalgia. Patients with PTLDS do not have objective synovitis as is seen Lyme arthritis patients.

Other autoimmune or autoinflammatory arthritides, such as rheumatoid arthritis, reactive arthritis, or psoriatic arthritis may develop within months after Lyme disease.[35] Although these events may be coincidental, it is possible that latent autoimmunity may be triggered by adjuvant or other immune effects of spirochetal infection. Since antibody responses to *B. burgdorferi* following antibiotic-treated Lyme arthritis typically persist for many years, positive serologic results can present a diagnostic challenge if these patients subsequently develop another type of arthritis.[36]

PHYSICAL EXAMINATION

Patients with Lyme arthritis typically have the following features on physical examination:

- Monoarthritis or oligoarthritis most commonly affecting the knees, but other large or small joints may be affected, such as an ankle, shoulder, elbow, or wrist.
- Affected knees may have very large effusions with warmth, but in contrast with typical bacterial (e.g., staphylococcal) septic arthritis, they are not particularly painful with range of motion or weight bearing. Baker's cysts may be present in the knees given the large size of effusions, and rupture of cysts is common.
- Fever is usually not present.

A photograph of typical knee swelling in Lyme arthritis is shown in Figure 2.

IMAGING AND ADDITIONAL TESTING

Serologic testing for Lyme disease

The mainstay in diagnosing Lyme arthritis is serologic testing. In the USA, the CDC currently recommends a two-test approach in which samples are first tested for antibodies to *B. burgdorferi* by enzyme-linked immunosorbent assay (ELISA) and those with equivocal or positive results are subsequently tested by a second assay, traditionally Western blotting (WB), with findings interpreted according to the CDC criteria.[37] Recently, the FDA approved the use of a second enzyme immunoassay (EIA) as an acceptable alternative to the Western blot, referred to as modified 2-tier testing.[38] However, for Lyme arthritis, the standard method involving an EIA followed by a Western blot provides more information and is preferred by the authors.

In contrast with early infection, when some patients may be seronegative, all patients with Lyme arthritis, have positive serologic results for IgG antibodies to *B. burgdorferi*, with expansion of the response to many spirochetal proteins.[39] Using microarrays, patients with Lyme arthritis have been shown to have IgG reactivity to as many as 89 spirochetal proteins.[40] Serologic testing should be performed only in serum, as Western blots of synovial fluid are not accurate.[41]

In addition to IgG antibody responses to *B. burgdorferi*, patients with Lyme arthritis may also have low-titer IgM reactivity with the spirochete. On the other hand, a positive IgM response alone in a patient with arthritis is likely to be a false-positive response or one indicative of previous, antibiotic-treated early Lyme disease in a patient who now has another type of arthritis. Therefore, positive IgM antibody responses alone should not be used to support the diagnosis of Lyme arthritis. After spirochetal killing with antibiotics, anti-spirochetal antibody titers decline gradually, but both the IgG and IgM responses in patients with past Lyme arthritis may remain positive for years,[36] which seems to be an indicator of immune memory rather than active infection. We have not observed re-infection in patients with the expanded immune response generated in patients Lyme arthritis. Therefore, a persistent, expanded IgG antibody response seems to be protective

against re-infection, whereas the limited antibody response seen in patients with erythema migrans is not.

Synovial Fluid PCR for *B. burgdorferi*

Although reported in a few patients,[42] it is exceedingly difficult to culture *B. burgdorferi* from synovial fluid in patients with Lyme arthritis. This is presumably due to the fact that joint fluid, with its many inflammatory mediators, is a hostile environment. In spiked cultures, adding small amounts of joint fluid results in rapid killing of spirochetes.[17] In contrast, polymerase chain reaction (PCR) testing of synovial fluid for *B. burgdorferi* DNA often yields positive results before antibiotic therapy (range, 40-96%),[19,43] and usually becomes negative following antibiotic treatment.[14] However, spirochetal DNA may persist for at least weeks after spirochetal killing, which limits its use as a test for active infection. Moreover, PCR testing has not been standardized for routine clinical use. Therefore, in most cases, the appropriate clinical picture and a positive serologic result are sufficient for diagnosis of Lyme arthritis, and PCR testing is an optional test to further support the diagnosis.

Synovial Fluid Analysis, Imaging and Other Tests

On presentation, joint aspiration is usually done for diagnostic purposes to rule out the presence of other arthritides such as crystalline arthropathy or staphylococcal septic arthritis. Joint fluid white cell counts are usually in an inflammatory range (10,000 to 25,000 cells/mm^3), but cell counts as low as 500 or as high as 100,000 cells/mm^3 have been reported.[3] Although tests for rheumatoid factor or antinuclear antibodies typically yield negative results, antinuclear antibodies in low titer may be detected. Peripheral white blood cell (WBC) counts are usually within the normal range, but inflammatory markers, such as ESR and CRP, may be elevated. An algorithm using elevated absolute neutrophil count >10,000 and ESR>40 mm/h, helped to distinguish septic monoarthritis from Lyme arthritis in pediatric patients in an endemic area.[44]

In LA patients, plain films, MRI scanning or ultrasound typically show non-specific joint effusions. With MRI and ultrasound studies synovial thickening and inflammation may be apparent. In adult patients, imaging studies may show co-incidental degenerative changes or chronic mechanical injuries, but these abnormalities would not be expected to cause significant synovitis or inflammation. Typical synovitis by ultrasound in an LA patient is shown in Figure 3. Lyme arthritis is not rapidly erosive, but with longer arthritis durations, joint damage can be seen on radiographic studies.[45,46] Imaging is not required for diagnosis, but may be useful in following response to treatment and determining extent of residual synovitis. In our clinic, we particularly use musculoskeletal ultrasound for this purpose. Finally, MRI scanning may be useful in the planning of synovectomies by determining the extent of synovitis within the joint.

Treatment

Treatment of Lyme arthritis is based on several small, double-blind or randomized studies and observational studies (summarized in Table 3). The efficacy of antibiotics was first demonstrated in a double-blind, placebo-controlled trial of IM benzathine penicillin, 2.4

million units weekly for 3 weeks versus placebo. In that study, 7 of 20 antibiotic-treated patients (35%) had complete resolution of arthritis, whereas all 20 placebo treatment patients continued to have arthritis.[47] Subsequently, 11 of 20 patients (55%) treated with IV penicillin, 20 million U daily in 6 divided doses for 10 days, had resolution of arthritis.[47] It was then reported that IV ceftriaxone, 2 g daily, was effective in 90% of patients who were given 2-4 weeks of therapy.[48] In a later randomized trial, treatment with 30 days of doxycycline, 100 mg twice daily, or amoxicillin, 500 mg four times daily, also led to resolution of arthritis in 90% of patients.[49]

According to current recommendations from the Infectious Diseases Society of America American Academy of Neurology, and American College of Rheumatology ,[50] patients with Lyme arthritis should be treated initially with a 28-day course of oral antibiotic, doxycycline, 100 mg twice daily, or amoxicillin, 500 mg three times daily. In patients who are unable to take either of these oral agents, cefuroxime axetil, 500 mg twice daily, may be an acceptable alternative. This medication was shown to be equivalent to treatment with doxycycline or amoxicillin in patients with EM,[51] but has not been studied systematically in patients with Lyme arthritis. Unless there are concomitant neurologic abnormalities, oral regimens are the initial treatment of choice as such therapy is safer and more cost effective.

In our experience, some patients do require longer courses of antibiotic therapy for effective treatment of Lyme arthritis.[14] Thus, if there is mild residual joint swelling after a 28-day course of oral antibiotics, we repeat the oral antibiotic regimen for another 28 days. However, for patients with minimal response and continued moderate-to-severe joint swelling after a 28-day course of oral antibiotics, it is recommended to treat with IV antibiotic which may have better tissue penetration, rather than a second course of oral antibiotic. Typically, we treat with IV ceftriaxone, 2gm/day. Although there is trend toward greater efficacy with 4 weeks compared with 2 weeks of antibiotics, there is also a greater frequency of adverse events.[52] Thus, our practice is to prescribe a 4-week course of IV therapy, but to monitor the patient closely and to stop treatment if complications occur.

Even in patients with minimal or no improvement with oral doxycycline, we typically observe moderate improvement or even complete resolution of arthritis with IV therapy. Moreover, even in those with persistent joint inflammation, the synovitis tends to change after IV therapy with decreased size of effusions but increased synovial tissue hypertrophy and continued inflammation. Courses longer than 30 days of IV antibiotics seem not to be beneficial and may be associated with greater adverse effects.[53] Additionally, a double-blind, randomized, placebo-controlled study of patients in Europe did not find a benefit of additional oral amoxicillin therapy following treatment with IV ceftriaxone.[54] While bacterial “persisters” have been observed in culture and in some animal studies, it is not clear that alternative antibiotic regimens targeting spirochetal persisters would be beneficial in post-antibiotic syndromes. [22]

Adjunctive therapy

During antibiotic treatment, non-steroidal anti-inflammatory agents (NSAIDs), such as ibuprofen or naproxen, may be used for pain. We do not use oral or intra-articular corticosteroids prior to or during antibiotic treatment, since these drugs may permit greater

growth of spirochetes[55] and may be associated with a worse outcome.[14,15] Moreover, we use them only sparingly after antibiotic treatment. When joints are inflamed, reduction of activity is important. If patients are limping, we advise crutch walking. Children may be more likely to regain normal function within 4 weeks after the initiation of antibiotic treatment,[32] but especially in adults, inflamed joints typically lead to quadriceps atrophy. Therefore, following the completion of antibiotic treatment and resolution of joint inflammation, formal physical therapy is often needed.

Therapy for Post-antibiotic Arthritis

The algorithm that we use for the diagnosis and treatment of LA and post-antibiotic arthritis is shown in Figure 4.[14] If synovitis persists following two or more months of oral antibiotics and one month of IV antibiotics, we employ a similar approach to that used in the treatment of other forms of chronic inflammatory arthritis, including rheumatoid arthritis and reactive arthritis. The agents used include NSAIDs, such as ibuprofen or naproxen, and DMARDs, typically methotrexate, depending on the severity of arthritis. Although there have been no formal trials with these agents, in practice, they reduce severity of inflammation and have not resulted in break-through cases of active infection. We generally do not give oral corticosteroids. The role of intra-articular steroids following antibiotic treatment is unclear, though some studies in children have found benefit.[56-57] In our experience, intra-articular injections of corticosteroids may have clinical utility as bridge therapy when starting DMARDs, but alone do not usually lead to sustained improvement.

In more recent years, with greater experience using more potent DMARD agents, we have developed an enhanced treatment strategy, now more commonly choosing low-dose methotrexate (MTX), typically 15-20 mg/week, over hydroxychloroquine as the initial DMARD, and reserving hydroxychloroquine , typically 400mg daily, for cases with milder synovitis. Moreover, in a few patients who had incomplete responses to MTX or in those with contraindications to MTX, we have used TNF inhibitors, generally injectable forms such as etanercept or adalimumab.[14] The onset of action of MTX and other DMARDs can be slow, but we generally see a significant response in 1-3 months. Since post-antibiotic arthritis eventually resolves in all LA patients,[14] long courses of DMARD therapy are generally not needed. We typically prescribe these medications for only 6-12 months rather than indefinitely as in the treatment of patients with rheumatoid arthritis. If the response to a DMARD agent is incomplete and if the arthritis is limited to one joint, primarily the knee, arthroscopic synovectomy is an option.[58].

Finally, though post-antibiotic LA is the major post-infectious complication, we occasionally see patients with the diffuse pain, neurocognitive or fatigue symptoms of PTLDS following Lyme arthritis. In addition, we occasionally see patients with Lyme arthritis who subsequently develop other forms of inflammatory arthritis.[35]

SUMMARY

In the United States, arthritis is the major late manifestation of Lyme disease, usually beginning months after the tick bite. However, because of greater recognition and treatment of early disease which prevents later arthritis, a history of EM or other early disease

manifestations is now often lacking in patients with Lyme arthritis. Patients have intermittent or persistent attacks of joint swelling and pain, primarily in one or a few large joints, often the knee, during a period of months to several years, with few systemic manifestations. The diagnosis is established by two-tier serologic testing for *B. burgdorferi* by ELISA and IgG Western blotting, which typically shows strong responses to many spirochetal proteins with many bands present. PCR testing of synovial fluid for *B. burgdorferi* DNA is often positive prior to antibiotic therapy, but the test is not a reliable indicator of spirochetal eradication following antibiotic treatment. Initial recommended therapies include a 30-day course of oral doxycycline or amoxicillin. However, for patients with minimal or no response to oral therapy, IV ceftriaxone for 2 to 4 weeks may be needed for successful treatment. A small percentage of patients may have persistent arthritis for months or several years after both oral and IV antibiotic therapy, which may be treated successfully with anti-inflammatory agents, DMARDs or synovectomy, depending on the severity of the arthritis. The antibody response to *B. burgdorferi* declines slowly after treatment, but the test typically remains positive for years after therapy.

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KEY POINTS

- Lyme arthritis is a late disease manifestation, usually beginning months after the tick bite.
- Patients have intermittent or persistent attacks of joint swelling and pain, in one or a few large joints, especially the knee, without prominent systemic manifestations.
- The diagnosis is supported by 2-tier serologic testing for *B. burgdorferi* by ELISA and IgG Western blotting.
- Initial treatment is a 30-day course of oral doxycycline or amoxicillin. For patients with minimal or no response to oral treatment, IV therapy with ceftriaxone is recommended.
- A minority of patients may have persistent synovitis for months or several years after oral and IV antibiotic therapy, which may be caused by excessive inflammatory immune responses and is treated with anti-inflammatory agents, DMARDs, or synovectomy.

SYNOPSIS

Arthritis is the most common late manifestation of *Borrelia burgdorferi* infection in the United States, usually beginning months after the tick bite. In most patients with Lyme arthritis today, arthritis is the presenting manifestation of the disease. Patients have swelling and pain in one or a few large joints, especially the knee. Serologic testing is the mainstay of diagnosis. Responses to antibiotic treatment are generally excellent, although a small percentage of patients have persistent, post-infectious synovitis after 2-3 months of oral and IV antibiotics, which responds to anti-inflammatory therapies. Herein we review the clinical presentation, diagnosis, and management of Lyme arthritis.

CLINICS CARE POINTS

- The diagnosis of Lyme arthritis is based on a positive IgG antibody response in blood. IgM positivity may also be present, but it is not required for the diagnosis. IgM positivity alone, without the presence of IgG antibodies, does not support of a diagnosis of Lyme arthritis.
- A positive PCR test in synovial fluid is an optional test but is not required for the diagnosis of Lyme arthritis. PCR testing may remain positive for weeks or longer after spirochetal killing and is not a reliable marker for active infection.
- Antibody responses to *Borrelia burgdorferi* may remain positive for many years after successful treatment of Lyme arthritis. Resolution of the serologic response cannot be used as criteria for successful treatment of the infection.
- The diagnosis of Lyme arthritis should be considered in patients from endemic areas presenting with a monoarticular or oligoarticular arthritis, whether or not there is any history of an antecedent tick bite or EM rash.
- Lyme arthritis is most commonly a mono or oligoarticular arthritis affecting one of both knees and does not manifest as a symmetrical polyarthritis such as rheumatoid arthritis.
- Patients with post-antibiotic Lyme arthritis respond well to DMARD therapy without recurrence of infection.

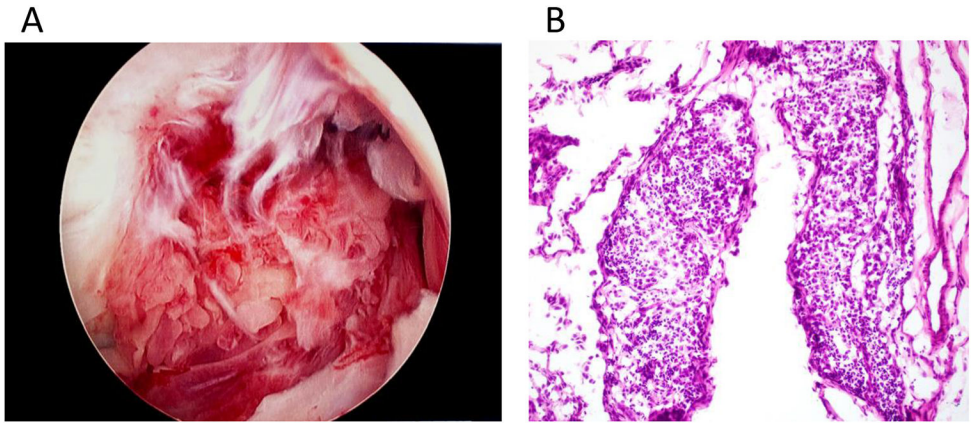

Figure 1.

Post-antibiotic Lyme arthritis synovium. In A. an image of post-antibiotic Lyme arthritis at arthroscopic synovectomy is shown, demonstrating vascular proliferation and synovial hypertrophy. In B. The histology of synovial tissue is shown in a patient post-antibiotic Lyme arthritis highlighting two villi with dense inflammatory infiltrate along the synovial lining and sublining layer. The section is stained with haematoxylin and eosin and shown at 20X magnification.

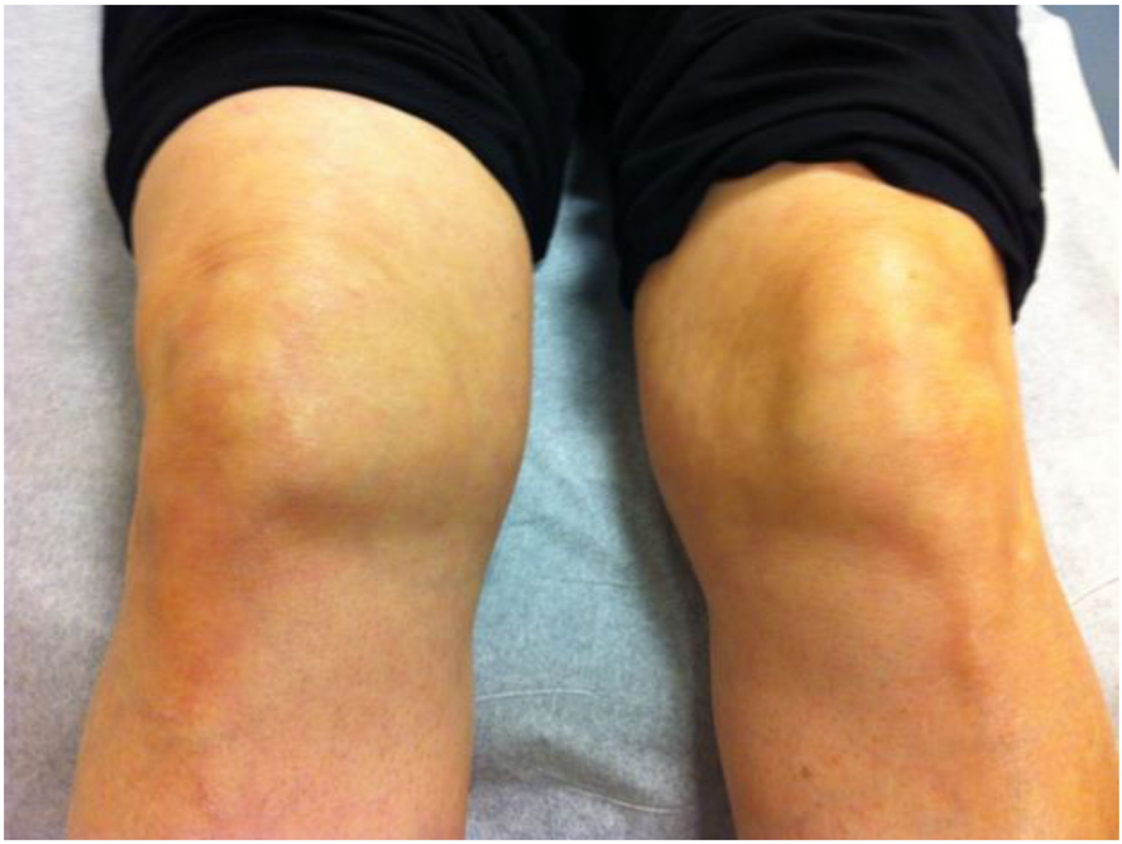

Figure 2.
Lyme arthritis. A swollen knee of a patient with Lyme arthritis is shown.

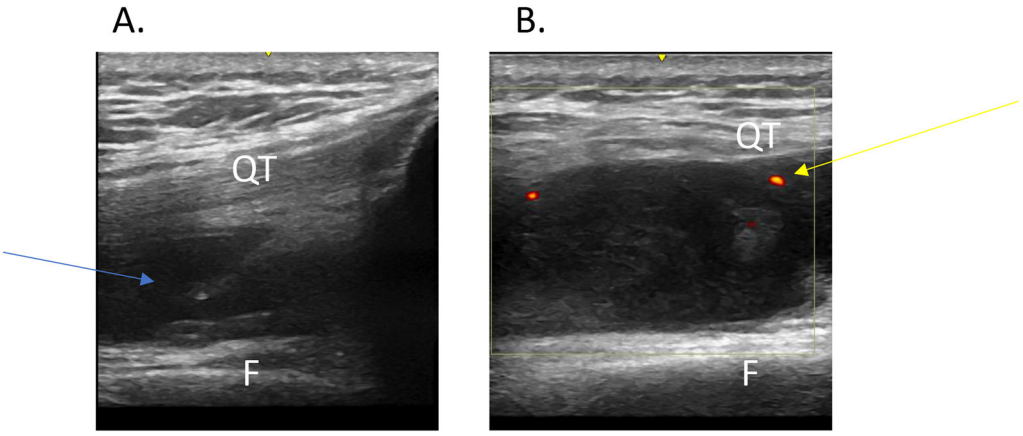

Figure 3.

Ultrasound image of Lyme arthritis. Longitudinal suprapatellar view (along long axis of quadriceps tendon) of left knee is shown. In A. anechoic effusion is noted by blue arrow. Proximal continuation is shown in B, with large effusion distending suprapatellar recess, synovitis (gray material), and Doppler signal (yellow arrow). QT=quadriceps tendon; F=femur. (*Courtesy of* Minna Kohler, MD, Boston, MA)

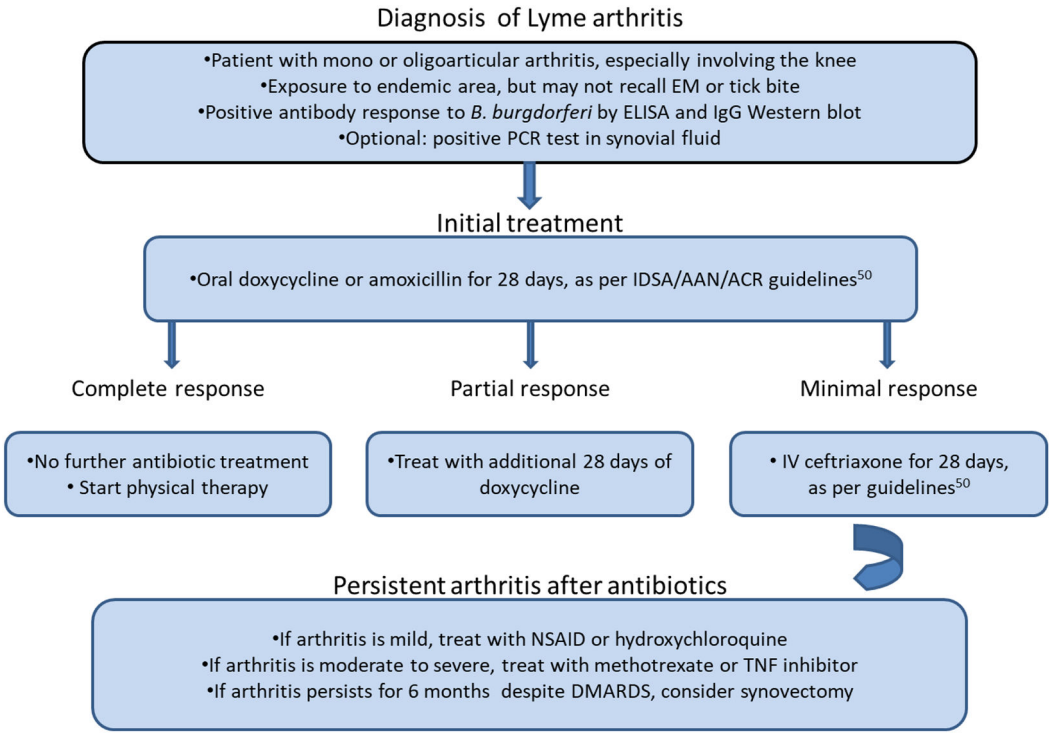

Figure 4.

Algorithm for the diagnosis and treatment of Lyme arthritis. EM = erythema migrans; ELISA = enzyme-linked immunosorbant assay; PCR = polymerase chain reaction; IDSA = Infectious Disease Society of America; AAN = American Academy of Neurology; ACR = American College of Rheumatology; IV= intravenous; NSAID = nonsteroidal antinflammatory drug; DMARDs = disease modifying anti-rheumatic drugs

Table 1.

Factors Associated with Post-antibiotic Lyme arthritis

Pathogen
• Infection with highly inflammatory RST-1 type strain[9]
• Possible retained spirochetal antigens such as peptidoglycan[12,20, 21]
Genetic
• Certain HLA-DR alleles[24]
• TLR1-1805GG polymorphism[23]
Immunologic
• Excessive inflammatory response with high amounts of IFN-gamma[18]
• Inadequate amounts of the anti-inflammatory cytokine IL-10[18]
• Decreased ratio of Treg/Teff cells among synovial fluid mononuclear cells[26,27]
• Lyme-associated autoantibodies[27-30]

Table 2.

Differential Diagnosis of Lyme arthritis

Diagnosis	Distinguishing Clinical Features	Helpful Laboratory Tests
Septic arthritis	Significant pain with range of motion, fever	synovial fluid culture
Gonococcal arthritis	Tenosynovitis, fever, pustular rash	synovial fluid culture
Crystalline arthritis	Significant pain with range of motion, history of podagra	Synovial fluid crystals
Rheumatoid arthritis	Symmetrical polyarthritis (5 or more joints involved),	RF and CCP
Juvenile idiopathic arthritis	May have polyarthritis, enthesitis, psoriasis	ANA, RF, CCP
Reactive arthritis	Preceding gastrointestinal, genitourinary or respiratory infection, enthesitis, eye involvement, rashes	HLA-B27
Ankylosing spondylitis, Psoriatic arthritis or other spondyloarthropathy	Axial (spine, sacroiliac joint) symptom, psoriasis, enthesitis,	HLA-B27
Fibromyalgia	Diffuse pain, lack of synovitis	ESR/CRP (normal)
Post-treatment Lyme disease syndrome	Non-specific pain, fatigue and neurocognitive symptoms, lack of synovitis	ESR/CRP (normal)
Autoimmune/Inflammatory arthritis triggered by Lyme	History of treated Lyme disease, polyarthritis, psoriasis, spondyloarthropathy features, axial involvement	RF/CCP antibodies, HLA-B27, *B. burgdorferi* antibodies (low titer)

Table 3:

Prospective Studies of Antibiotic Therapy in Lyme arthritis

Author	Year	Trial type/Treatment	Patients	Outcomes
Steere et al.[47]	1985	Double-blind, placebo-controlled trial of intramuscular benzathine penicillin (PCN) for 3 weeks vs. placebo	40 with Lyme arthritis	7/20 (35%) PCN treated patients had complete response versus 0/20 in placebo arm (P=0.02)
		Additional 20 patients received IV PCN 20 million units/day for 10 days	20 with Lyme arthritis	11/20 (55%) had complete resolution
Dattwyler et al.[48]	1988	Randomized to IV treatment with PCN (10 days) or ceftriaxone (CTX) (14 days)	23 patients with late Lyme (16 with arthritis)	5/10 responded toPCN versus 12/13 responded to CTX
		Additional non-randomized cohort treated with CTX 2 or 4g	31 patients (23 with arthritis)	27/31 patients responded to CTX
				Overall >90% response to CTX
Steere et al.[49]	1994	Randomized trial of doxycycline or amoxicillin plus probenecid for30 days, Or 2 weeks of IV CTX for patients with persistent arthritis 3 mos after oral antibiotics or PCN	50 with Lyme arthritis	18/20 patients receiving doxycycline and 16/18 receiving amoxicillin had complete response by 3 months. 5 patients later developed neuroborreliosis.
				0/16 patients treated with IV CTX had resolution with 3 mos.
Dattwyler et al.[52]	2005	Randomized trial of CTX, 14 vs.28 day regimen	143 patients with late Lyme disease	5 failures out of 80 patients in 14-day group, but 0 failures out of 63patients in 28-day group (P=0.07).
				Increased adverse events in 28-day group (P=0.02)
Oksi et al.[54]	2007	Double-blind randomized placebo controlled trial of adjunct oral antibiotic therapy (amoxicillin) vs. placebo for 100 days following 3 weeks of IV CTX	107 patients with definite disseminated Lyme disease, including 45 with arthritis	Excellent/good response in 49/53 in amoxicillin group and 47/54 in placebo treated groups (NS). 37/45 Lyme arthritis patients had excellent or good responses.

Abbreviations: Penicillin (PCN), intravenous (IV), ceftriaxone (CTX)