

## REVIEW

# Therapy for Lyme Arthritis

## Strategies for the Treatment of Antibiotic-Refractory Arthritis

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### Introduction

Lyme arthritis, caused by the tick-borne spirochete *Borrelia burgdorferi* (1), typically causes intermittent or persistent arthritis in a few large joints, especially the knee, for several years (2). Treatment recommendations have changed over time. In the early 1980s, 3 intramuscular injections of benzathine penicillin or a 10-day course of high-dose intravenous (IV) penicillin cured only 35–55% of patients (3). In the late 1980s, treatment with IV ceftriaxone for 2 weeks was effective in ~90% of patients (4,5); slightly better results were achieved with 4 weeks of therapy (6), but adverse events occurred more frequently. During the same period of time, a 4-week course of oral doxycycline or amoxicillin was also effective in ~90% of patients with Lyme arthritis (7). However, joint swelling in some patients remained unresponsive to oral therapy and re-treatment with a 2-week course of IV ceftriaxone (7). To date, little information is available about therapy for such patients. One non-antibiotic-treated patient had resolution of joint swelling following hydroxychloroquine therapy (8). Sixteen of 20 patients with persistent arthritis despite antibiotic therapy experienced resolution after arthroscopic synovectomy (9).

In 2000, an expert panel from the Infectious Diseases Society of America (IDSA) presented guidelines for the treatment of Lyme disease (10). The panel

recommended initial treatment with oral doxycycline or amoxicillin for 4 weeks for patients with Lyme arthritis and no concomitant neurologic abnormalities. Results of a cost-benefit analysis suggested that such therapy is as effective as IV therapy, is safer than IV therapy, and is considerably less expensive (11). For patients in whom arthritis is persistent despite receiving 4 weeks of oral antibiotic therapy, the panel recommended re-treatment with another 4-week course of oral antibiotics or with a 2–4-week course of IV ceftriaxone. However, in a small percentage of patients, proliferative synovitis (12,13) persists for months to several years, even after  $\geq 2$  months of treatment with oral antibiotics,  $\geq 1$  month of treatment with IV antibiotics, or both, which we have termed antibiotic-refractory (or slowly resolving) Lyme arthritis.

### Pathogenesis of antibiotic-refractory Lyme arthritis

Antibiotic-refractory Lyme arthritis may result from persistent infection (14) or from postinfectious immune phenomena (15). Although there are only 2 case reports of successful cultivation of *B burgdorferi* from affected joints (16,17), results of detection of *B burgdorferi* DNA in joint fluid by polymerase chain reaction (PCR) are usually positive prior to antibiotic therapy (18,19) and are often negative after 2 months of therapy with oral antibiotics or 1 month of therapy with IV antibiotics (18). Because positive results of PCR in synovial tissue may occur when PCR results in joint fluid are negative (20), negative results in joint fluid do not exclude the possible survival of small numbers of spirochetes. However, persistent infection is likely not an explanation for antibiotic-refractory arthritis in most patients, because PCR results were negative in synovial samples obtained from all 26 patients who had arthroscopic synovectomies a median of 7 months after receiving antibiotic therapy (21).

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In murine Lyme arthritis, *B burgdorferi* could not be cultured from organs and tissues after 5–10 days of ceftriaxone treatment, even if the animals were immunosuppressed with corticosteroids (22). In mouse and dog models, residual positivity of PCR results was sometimes demonstrable for months after a 30-day course of doxycycline or ceftriaxone (23,24). However, even with immunosuppression, the animals remained culture negative and did not have synovial inflammation. Thus, it is likely that 2–3 months of antibiotic therapy in humans results in near or total eradication of viable spirochetes from affected joints.

The first suggestion that antibiotic-refractory Lyme arthritis may have an autoimmune component was the demonstration of its association with the HLA-DR4 and HLA-DR2 alleles (25). Patients who have HLA-DRB molecules that bind an epitope of *B burgdorferi* outer surface protein A (OspA<sub>163–175</sub>) are more likely to have antibiotic-refractory arthritis than are patients with other DRB molecules (26). Molecular techniques have identified the OspA<sub>163–175</sub>-binding molecules as the rheumatoid arthritis (RA) alleles (DRB1\*0401, 0404, 0405, 0101, 0102) (27,28) and the DRB5\*0101 allele linked to DRB1\*1501 (the former DR2 allele) (26). Moreover, patients with antibiotic-refractory arthritis often have T cell recognition of OspA<sub>163–175</sub> (29–33). Because this epitope does not occur in the more common causative agents of Lyme borreliosis in Europe, *Borrelia afzelii* and *Borrelia garinii* (32), this mechanism may apply primarily to American patients with antibiotic-refractory Lyme arthritis.

Human lymphocyte function-associated antigen 1 $\alpha_{L332-340}$  (LFA-1 $\alpha_{L332-340}$ ), which has partial sequence homology with OspA<sub>163–175</sub>, has been proposed as a candidate autoantigen in antibiotic-refractory Lyme arthritis (29). However, the LFA-1 peptide is only a weak, partial agonist for OspA<sub>163–175</sub>-reactive T cells, even in patients with the DRB1\*0401 molecule (34), and the LFA-1 peptide does not bind the antibiotic-refractory arthritis-associated DRB1\*0101 molecule (35), making it unlikely to be a relevant autoantigen in this illness.

During acute Lyme arthritis, the levels of proinflammatory cytokines in joint fluid (tumor necrosis factor  $\alpha$ , interleukin-1 $\beta$ , and interferon- $\gamma$ ) were higher in patients with antibiotic-refractory arthritis than in patients with antibiotic-responsive arthritis (36,37). During the post-antibiotic treatment period, when results of tests for *B burgdorferi* DNA were uniformly negative, patients with antibiotic-refractory disease have sustained or even higher levels of proinflammatory cytokines in joint fluid and synovial tissue (36). Thus, recognition of

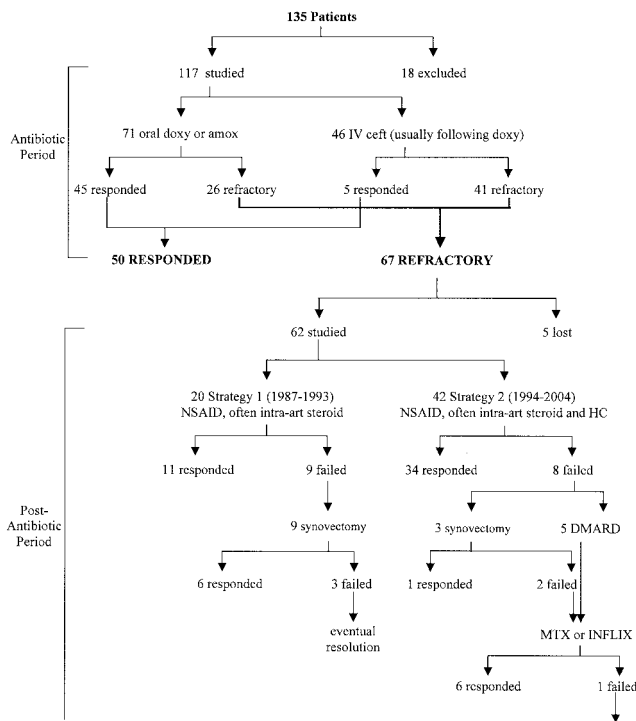
the OspA<sub>163–175</sub> epitope (or other unidentified epitopes) may lead to especially high levels of proinflammatory cytokines, which may not be appropriately down-regulated as spirochetal killing progresses. Alternately, high levels of inflammatory cytokines could lead to the breaking of tolerance to a currently unidentified self epitope, which may continue to elicit synovial inflammation after spirochetal eradication.

We favor the hypothesis that in most patients, synovial inflammation persists after the near or total eradication of spirochetes. Therefore, in patients in whom IDSA-recommended courses of antibiotic therapy fail, we treat with antiinflammatory agents. In the following sections, we compare findings and therapy in patients with antibiotic-responsive arthritis and those with antibiotic-refractory arthritis, in an effort to identify risk factors for a refractory course. In addition, we present our experience with post-antibiotic treatment strategies.

#### Experience treating patients with antibiotic-refractory arthritis

**Patients.** From November 1987 (when IV ceftriaxone and oral doxycycline or amoxicillin began to be used for the treatment of Lyme arthritis) through May 2004, we evaluated 135 patients with Lyme arthritis (ages 12 years or older). All 135 patients met the Centers for Disease Control and Prevention (CDC) criteria for the diagnosis of Lyme arthritis (38). All patients had monarticular or oligoarticular arthritis and a positive antibody response to *B burgdorferi* by enzyme-linked immunosorbent assay and Western blotting (39), as interpreted according to the CDC criteria (40). The majority of patients in whom joint fluid was tested by PCR prior to or during antibiotic therapy also had a positive result for *B burgdorferi* DNA using primer-probe sets that target the OspA or OspB gene of the spirochete (18). The same protocol, which was approved by the Internal Review Board at New England Medical Center (from 1987 to 2002) or Massachusetts General Hospital (from 2002 to 2004), was used to evaluate all patients.

As shown in Figure 1, of 135 patients screened, 117 were included in the analysis. Reasons for exclusion included the following: antibiotic therapy did not meet the current IDSA guidelines (n = 4), the patient had degenerative arthritis in the affected knee (n = 3), followup evaluations were inadequate to determine responses to antibiotic therapy (n = 7), and referral occurred too late to allow evaluation (n = 4). Fifty patients had antibiotic-responsive arthritis (i.e., resolu-



**Figure 1.** Flow chart showing characteristics of and outcomes in patients in the study population. doxy = doxycycline; amox = amoxicillin, IV = intravenous; ceft = ceftriaxone, NSAID = nonsteroidal antiinflammatory drug; intra-art = intraarticular; HC = hydroxychloroquine; DMARD = disease-modifying antirheumatic drug; MTX = methotrexate; INFLIX = infliximab.

tion of arthritis within 3 months after no more than 4 weeks of IV antibiotic therapy or 8 weeks of treatment with oral antibiotics (10), and 67 patients had antibiotic-refractory arthritis (i.e., persistent joint swelling for  $\geq 3$  months after the start of at least 4 weeks of IV antibiotic therapy or at least 8 weeks of oral antibiotic therapy, or both). Of the 55 patients who were referred before or during their first course of antibiotics, 50 (91%) had antibiotic-responsive arthritis, and 5 had an antibiotic-refractory disease course; this distribution is similar to that in the community (7). Of the 67 patients with antibiotic-refractory arthritis, 62 were referred because of an inadequate response to 1 or more courses of antibiotics. This skewed distribution (67 patients with antibiotic-refractory arthritis compared with 50 patients with antibiotic-responsive arthritis) is reflective of our role as a referral center.

**Post-antibiotic treatment.** After antibiotic therapy, patients seen from November 1987 through December 1993 received treatment with nonsteroidal antiin-

flammatory drugs (NSAIDs) or intraarticular corticosteroids, or, if the arthritis persisted for 12–24 months, with arthroscopic synovectomy (strategy 1). In 1994, after PCR testing of joint fluid for *B burgdorferi* DNA became available (18), disease-modifying antirheumatic drugs (DMARDs), particularly hydroxychloroquine, were added to this regimen in patients who had negative results of PCR and persistent arthritis (strategy 2). If arthritis did not improve, DMARD therapy was changed to treatment with oral methotrexate for 3–4 months or, when it became available, to IV infliximab (2–4 infusions). If the arthritis still persisted, arthroscopic synovectomy was performed.

### Risk factors for an antibiotic-refractory course

**Pretreatment.** Patients with antibiotic-responsive or antibiotic-refractory arthritis ranged in age from 12 years to 79 years; the sex ratio was slightly in favor of men (Table 1). Only about one-fourth of the patients had erythema migrans. Instead, most patients presented with marked swelling and pain in 1 or both knees, occasionally accompanied by neurologic signs or symptoms. The median duration of joint swelling prior to the diagnosis of arthritis was  $\sim 1$  month (Table 1). During that period, patients with antibiotic-refractory arthritis tended to receive intraarticular corticosteroids more often than did patients with antibiotic-responsive arthritis, but the duration of subsequent arthritis was similar in patients who did receive this treatment and in those who did not.

**Antibiotic treatment.** In patients with antibiotic-responsive arthritis, a 1-month course of oral doxycycline was usually successful (Table 2). In contrast, patients with antibiotic-refractory arthritis usually had persistent disease despite a 2-month course of treatment with oral doxycycline followed by a 1-month course of IV ceftriaxone. However, the type of antibiotic therapy (oral therapy alone, oral therapy followed by IV therapy, or IV treatment alone) did not correlate with the subsequent duration of arthritis.

**Laboratory analysis.** Prior to or during antibiotic therapy, 10 of 19 patients with antibiotic-responsive arthritis (53%) and 15 of 25 patients with antibiotic-refractory arthritis (60%) had positive PCR results for the detection of *B burgdorferi* DNA in joint fluid. Of 34 patients with antibiotic-refractory arthritis in whom joint fluid was available for testing after antibiotic therapy, 2 (6%) had a positive PCR result after 4–5 months, and 1 still had a weakly positive result at 6 months. By the end of antibiotic treatment, all patients with antibiotic-refractory arthritis who were tested had negative PCR

**Table 1.** Clinical characteristics of patients with Lyme arthritis prior to antibiotic therapy\*

Characteristic	Antibiotic responsive (n = 50)	Antibiotic refractory (n = 67)
Age, median (range) years	45 (12–74)	36 (12–79)
No. of men/no. of women (sex ratio)	30/20 (1.5)	43/24 (1.8)
Early signs or symptoms		
Erythema migrans	13 (26)	14 (21)
Flu-like illness alone	7 (14)	12 (18)
Joints affected		
1 knee	45 (90)	51 (76)
Both knees	5 (10)	16 (24)
1 or 2 large joints in addition to the knee†	8 (16)	5 (7)
Duration of active arthritis prior to antibiotic treatment, median (range) months	1.4 (0.25–25)	1 (0.25–30)
Intraarticular steroid injection prior to antibiotic treatment	7 (14)	19 (28)‡
Concomitant neurologic symptoms§	3 (6)	10 (15)

\* Except where indicated otherwise, values are the number (%) of patients.

† Additional joints affected included the wrist, elbow, shoulder, ankle, or temporomandibular joint.

‡  $P = 0.1$  versus the antibiotic-responsive group. No significant difference between the groups was observed at the 0.05 level.

§ Three of the 10 patients with antibiotic-refractory arthritis and 1 of the 3 patients with antibiotic-responsive arthritis were diagnosed as having encephalopathy or polyneuropathy by cerebrospinal fluid analysis or electromyography; the remaining patients reported memory difficulty or paresthesias, but they did not undergo formal testing for neuroborreliosis.

results. The median titer of IgG antibody to *B burgdorferi* was slightly higher in patients with refractory arthritis (1:12,800) than in those with antibiotic-responsive arthritis (1:6,400), but this difference was not statistically significant. Patients with antibiotic-refractory arthritis were more likely to have HLA-DR molecules that bound the OspA<sub>163–175</sub> epitope of *B burgdorferi* (26). Patients with antibiotic-refractory arthritis and those with

antibiotic-responsive arthritis were previously shown to differ in terms of their cellular and humoral immune responses to OspA (7,30). Thus, risk factors for antibiotic-refractory arthritis include specific HLA-DRB1 alleles, greater immune reactivity with OspA, and, perhaps, treatment with intraarticular steroids prior to antibiotic therapy.

**Table 2.** Antibiotic therapy in patients with antibiotic-responsive or antibiotic-refractory Lyme arthritis\*

	Antibiotic responsive (n = 50)	Antibiotic refractory (n = 67)
Type of therapy, no. (%) of patients		
Oral doxycycline (100 mg bid) or amoxicillin (500 mg tid)	44 (88)	26 (39)
Oral doxycycline or amoxicillin, followed by IV ceftriaxone (2 gm/day) or IV antibiotic therapy alone	6 (12)	41 (61)
Total duration of therapy, median (range) weeks		
Oral therapy alone	4 (4–8)	8 (8–52)
IV therapy, with or without oral therapy	8 (4–8)	12 (4–29)

\* In 3 patients with antibiotic-refractory arthritis who had adverse reactions to intravenous (IV) ceftriaxone, the course of treatment was completed with IV cefotaxime (2 gm 3 times daily [tid]) or IV penicillin (5 million units, 4 times daily). Only 1 patient in each group received IV therapy alone. The number of patients who received IV therapy was significantly higher ( $P < 0.001$ ) in the antibiotic-refractory group than in the antibiotic-responsive group. There were no other significant differences between the groups. bid = twice daily.

### Post-antibiotic treatment strategies in patients with antibiotic-refractory arthritis

**First strategy.** Figure 1 and Tables 3 and 4 indicate the therapy for and outcomes of patients treated according to strategies 1 and 2. Among the 22 patients treated according to strategy 1, 2 were lost to followup. Of the 20 patients in whom the total duration of arthritis was known, 11 (55%) had resolution of arthritis within a median of 11 months after the initiation of antibiotics. The 9 remaining patients underwent arthroscopic synovectomies; in the 8 patients who were tested, synovial tissue was negative for *B burgdorferi* DNA. Rehabilitation often required months, and lysis of adhesions under anesthesia was sometimes necessary to regain mobility of the joint. Arthritis eventually resolved in all patients within a median of 14 months (range 4–42 months) after the start of antibiotic therapy.

**Second strategy.** Among the 45 patients treated according to the second strategy, 3 were lost to followup

**Table 3.** Post-antibiotic therapy in 22 patients treated according to strategy 1\*

	No. (%) of patients	Median (range) months from initiation of antibiotics to start of indicated therapy
Antiinflammatory agents		
NSAIDs†	19 (86)	3 (1–10)
1 or 2 intraarticular steroid injections‡	18 (82)	7 (3–32)
Arthroscopic synovectomy	9 (41)	12 (6–30)
Persistent arthritis after synovectomy§	3 (14)	–

\* Two of the 22 patients were lost to followup during treatment with nonsteroidal antiinflammatory drugs (NSAIDs) or intraarticular steroids.

† Ibuprofen, 400 mg 3 times daily, naproxen, 375 mg twice daily, or diclofenac, 50–75 mg twice daily. Patients received NSAIDs for a median of 6 months (range 3–24 months).

‡ Triamcinolone hexacetonide, 40 mg or 80 mg. Six of the 18 patients also received intraarticular steroids prior to antibiotic therapy.

§ Synovitis persisted for 9, 15, and 19 months, respectively, after the procedure.

(Figure 1 and Table 4). Of the 42 remaining patients, 34 (81%) had resolution of arthritis within a median 8 months after the start of antibiotic therapy. Three of the remaining 8 patients with persistent arthritis elected to have arthroscopic synovectomies, but the procedure was successful in only 1 of them (this patient, who received

oral antibiotics for only 2 months, was the only one who had a positive PCR result for *B burgdorferi* DNA in synovial tissue obtained during synovectomy). The 2 patients who had persistent arthritis despite synovectomy and the 5 patients who did not respond to hydroxychloroquine were treated with methotrexate or with 2–4 infusions of infliximab. Most of these patients responded to either medication, but the results were more dramatic with infliximab. All 4 patients treated with this medication had marked reductions in joint inflammation. However, 1 of these patients experienced worsening after the medication was stopped but responded to synovectomy. *B burgdorferi* DNA was not detected in synovial tissue. In total, arthritis in the 42 patients persisted for a median of 9 months (range 4–44 months) after the start of antibiotic therapy.

**Recurrent arthritis.** In all patients, NSAIDs and DMARDs were discontinued after disease remission was achieved. Within several months, arthritis recurred in 3 of the 25 patients treated with oral antibiotics (12%) and in none of the 37 patients treated with IV antibiotics. During recurrent episodes, 2 patients who had received NSAIDs in the post-antibiotic period had negative PCR results for *B burgdorferi* DNA in joint fluid but were re-treated with oral doxycycline for 30 days, with resolution occurring within several weeks. The third patient, who had received hydroxychloroquine in the

**Table 4.** Post-antibiotic therapy in 45 patients treated according to strategy 2\*

Treatment	No. (%) of patients	Median (range) months from start of antibiotics to start of indicated therapy	Median (range) months of indicated therapy
Antiinflammatory agents			
NSAIDs	39 (87)	3 (1–6)	5 (1–12)
1 or 2 intraarticular steroid injections†	29 (64)	6 (2–14)	–
Arthroscopic synovectomy	3 (7)	10, 13, 26	–
DMARD following synovectomy	2 (4)	–	–
Hydroxychloroquine, 200 mg twice daily‡	25 (56)	5 (3–19)	5 (3–19)
Methotrexate, 7.5–25 mg/week§	5 (11)	12 (5–15)	5 (4–7)
Infliximab, 3 mg/kg, 3–4 IV infusions¶	4 (9)	11 (16)	2 (1–4)
Synovectomy after infliximab	1 (2)	–	–

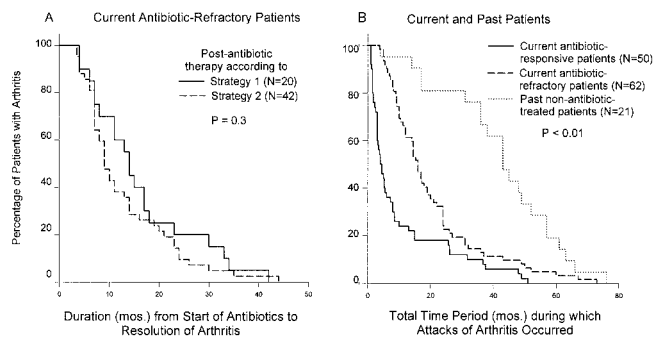
\* Three of the 45 patients were lost to followup treatment with nonsteroidal antiinflammatory drugs (NSAIDs) or intraarticular steroids. Patients were treated with the indicated disease-modifying antirheumatic drug (DMARD) until remission was achieved. However, if there was no or minimal response, the medication was changed to another DMARD. IV = intravenous.

† A total of 39 patients received intraarticular steroids prior to or after antibiotic therapy.

‡ Five patients did not respond to hydroxychloroquine and received either methotrexate (n = 3) or infliximab (n = 2).

§ Of the 5 patients who received methotrexate, 3 had failed to respond to hydroxychloroquine, and 2 had persistent arthritis after synovectomy.

¶ Infliximab infusions were administered at 0-, 2-, 4-, and 8-week intervals. The 4 patients who received infliximab had failed to respond to hydroxychloroquine (n = 2) or methotrexate (n = 2).



**Figure 2.** Duration from start of antibiotic therapy to resolution of arthritis, and total time period during which attacks of arthritis occurred. **A**, Rate of arthritis resolution among patients with antibiotic-refractory disease treated according to strategy 1 (nonsteroidal antiinflammatory drugs, intraarticular steroids, or arthroscopic synovectomy) or strategy 2 (disease-modifying antirheumatic drug, primarily hydroxychloroquine, added to regimen in strategy 1). The overall resolution rate was similar with both treatment strategies. **B**, Time during which attacks of arthritis occurred in all current patients with antibiotic-responsive or antibiotic-refractory arthritis and in historic patients seen in the late 1970s who were not treated with antibiotics for at least 4 years. The overall duration of joint inflammation was significantly shorter in patients with antibiotic-responsive or antibiotic-refractory arthritis than in patients who were not treated with antibiotics. The groups were compared by survival log rank test.

post-antibiotic period, was the only patient who had recurrent arthritis and a positive PCR result. She had 2 recurrences of arthritis, each of which was treated with IV antibiotics for 1 month.

**Comparison of the treatment strategies.** Most of the patients treated according to either strategy received NSAIDs and often 1 or 2 intraarticular injections of steroids. With both treatment strategies, the overall rate of arthritis resolution was similar, and the longest duration of arthritis was  $\sim 3.5$  years ( $P = 0.3$ ) (Figure 2A).

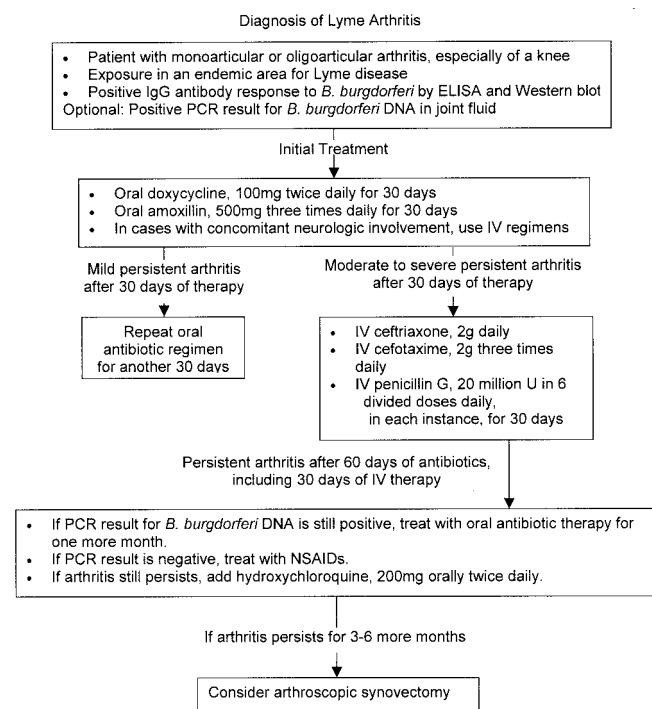
Because Lyme arthritis resolves eventually in all patients, even in those who do not receive antibiotic therapy (2), did treatment of patients with antibiotic-refractory arthritis alter the natural history of the illness? To address this question, we compared our early experience with non-antibiotic-treated patients with our experience with the current patients.

In the late 1970s, before the etiologic agent of Lyme disease was known, we followed up 21 patients with erythema migrans and Lyme arthritis (ages 12 years or older) for at least 4 years, without antibiotic treatment (2). These patients were treated with NSAIDs and intraarticular steroids, but not with synovectomies. A few patients had only 1 or 2 brief attacks of arthritis, but others had continuous synovitis for as long as 4 years,

along with shorter, intermittent episodes of joint swelling, during a total period as long as 8 years. Altogether, these 21 patients who were not treated with antibiotics had attacks of arthritis during a median total time period of 43 months (range 4–76 months), compared with the 50 patients with antibiotic-responsive disease who had episodes of arthritis during a median total time period of 4 months (range 1–51 months) and the 62 patients with antibiotic-refractory disease who had joint swelling during a median total period of 16 months (range 4–73 months) ( $P < 0.001$ ) (Figure 2B). Thus, we believe that antibiotic therapy decreases the period of joint inflammation, even in patients with antibiotic-refractory arthritis. In addition, it is our impression that DMARD therapy in the post-antibiotic period reduces the severity of joint inflammation, and breakthrough cases of active infection were not intensified except in 1 hydroxychloroquine-treated patient who received oral antibiotics for only 2 months.

### Approach to treatment

Antibiotic treatment remains the cornerstone of therapy for Lyme arthritis. Unless a patient has concom-



**Figure 3.** Algorithm for the diagnosis and treatment of Lyme arthritis. *B. burgdorferi* = *Borrelia burgdorferi*; ELISA = enzyme-linked immunosorbent assay; PCR = polymerase chain reaction; IV = intravenous; NSAIDs = nonsteroidal antiinflammatory drugs.

itant neurologic abnormalities, a 1-month course of oral doxycycline or amoxicillin is recommended (Figure 3). Most patients experience resolution of arthritis during the course of such therapy. However, if there is mild residual joint swelling, we repeat the oral antibiotic regimen for another 30 days, even though the arthritis usually resolves without further therapy (7). In our experience, no patient who received IV therapy had persistence of *B burgdorferi* DNA in joint fluid or synovial tissue or recurrent attacks of arthritis. Hence, if patients have moderate to severe joint swelling after a 1-month course of oral antibiotics, IV ceftriaxone (2 gm/day) for an additional month is appropriate. If arthritis persists and PCR results remain positive, we re-treat with oral antibiotics for an additional month, even though PCR results may remain positive in joint fluid for several weeks after the eradication of spirochetes (24,41).

If arthritis still persists, might longer courses of antibiotics be beneficial? Several of our patients received oral antibiotics for 6–12 months or IV antibiotics for 6–8 weeks, but joint swelling did not resolve. In addition, the longer the course of antibiotics, the greater the risk of adverse events. Seven of 37 patients (19%) who were treated for Lyme encephalopathy with IV ceftriaxone or placebo for 10 weeks had serious IV line complications, including sepsis (42). Thus, still longer courses of antibiotics are likely ineffective and may be dangerous.

For patients who have persistent arthritis after receiving oral doxycycline for 1 month and IV ceftriaxone for 1 month and who have negative PCR results for *B burgdorferi* DNA in joint fluid, we recommend NSAIDs and hydroxychloroquine, which may have both antispirochetal (43,44) and antiinflammatory effects (45). In our experience, breakthrough cases of persistent infection were not identified in DMARD-treated patients, except in 1 case. Although we have used more potent DMARDs, we are reluctant to recommend them, because our limited experience does not prove efficacy and because of the concern that they might be given to patients in whom infection is still active. Intraarticular corticosteroids given prior to antibiotics may be a risk factor for persistent Lyme arthritis (5,7) and, in animal models, are associated with higher spirochetal burdens and longer persistence of spirochetal DNA (22,46). Thus, intraarticular corticosteroids should not be given prior to antibiotic therapy, and we now rarely use them in the post-antibiotic period. If arthritis persists for more than 12 months, arthroscopic synovectomy remains an option. Although chronic Lyme arthritis may cause

functional disability with erosion of cartilage and bone (47,48), it resolves eventually in all patients.

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Therapy for Lyme arthritis: strategies for the treatment of antibiotic-refractory arthritis. *Arthritis Rheum* 2006; 54: 3079-86. 15. Steere AC, Klitz W, Drouin EE, et al. Antibiotic-refractory Lyme arthritis is associated with HLA-DR molecules that bind a *Borrelia burgdorferi* peptide. *J Exp Med* 2006; 203:961-71. 16. Nowakowski J, Nadelman RB, Sell R, et al. Therapy for Lyme arthritis: strategies for the treatment of antibiotic-refractory arthritis. *Arthritis Rheum* 2006;54:3079-3086 20. Steere AC, Klitz W, Drouin EE, Falk BA, Kwok WW, Nepom GT, Baxter-Lowe LA. Antibiotic-refractory Lyme arthritis is associated with HLA-DR molecules that bind a *Borrelia burgdorferi* peptide. *J Exp Med* 2006;203:961-971. 21. Wilske B, Fingerle V, Schulte-Spechtel U. Microbiological and serological diagnosis of Lyme borreliosis. Arthritis treatment focuses on relieving symptoms and improving joint function. You may need to try several different treatments, or combinations of treatments, before you determine what works best for you. Medications. The medications used to treat arthritis vary depending on the type of arthritis. This therapy uses fine needles inserted at specific points on the skin to reduce many types of pain, including that caused by some types of arthritis. Glucosamine. Although study results have been mixed, some studies have found that glucosamine works no better than placebo. Effectiveness and safety of glucosamine and chondroitin for the treatment of osteoarthritis: A meta-analysis of randomized controlled trials. *Journal of Orthopaedic Surgery and Research*. 2018;13:170. For the treatment of Lyme carditis, we suggest 14-21 days of total antibiotic therapy over longer durations of treatment (weak recommendation, very low-quality evidence). Comment: Oral antibiotic choices for Lyme carditis are doxycycline, amoxicillin, cefuroxime axetil, and azithromycin. XX. What is the preferred diagnostic testing strategy for Lyme arthritis? When assessing possible Lyme arthritis, we recommend serum antibody testing over PCR or culture of blood or synovial fluid/tissue (strong recommendation, moderate quality of evidence).