Antibiotic Therapy for Lyme Disease in Maryland

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Synopsis

The recommended treatment of Lyme disease is evolving and important questions remain unanswered, such as (a) Are inexpensive oral regimens effective in curing acute illness and preventing arthritic, neurologic, and cardiac manifestations or are much more costly, and potentially toxic, intravenous antibiotics required? (b) Are relatively short 2- to 3-week courses of antibiotics sufficient or are prolonged regimens of a month, or more, better? This study reviews antibiotic therapy prescribed by Maryland physicians for the 283 cases reported in 1991 that meet the Centers for Disease Control and Prevention's case definition for Lyme disease. The purpose of the review was to obtain baseline information on the antibiotics being used by physicians in practice to treat patients that they believe have Lyme disease.

The most frequently prescribed antibiotics for either the 60 percent of patients presenting with erythema migrans or the 40 percent with arthritic, neurologic, or cardiac manifestations were oral doxycycline (47 percent), tetracycline (11 percent), and amoxicillin (13 percent). Seventy-one percent of therapeutic courses were for 2 to 3 weeks. Amoxicillin was used in two-thirds of children younger than 8 years. Sixty (21 percent) received intravenous therapy, of which ceftriaxone, with or without other antibiotics, was almost always (95 percent) used. Intravenous therapy was more frequently given to those with arthritic, neurologic, and cardiac manifestations than to those with erythema migrans (odds ratio = 3.7) and to those with these systemic symptoms along with erythema migrans than to those with erythema migrans alone (odds ratio = 3.8). The average course was 2 days longer in treating those with arthritic, neurologic, or cardiac manifestations than in treating those with erythema migrans alone (P = 0.05).

An epidemiologic assessment of antibiotics prescribed by the physicians in Maryland to treat Lyme disease in 1991 shows the choices, dosage, and duration of drugs generally followed those most frequently recommended in the literature. Also, it shows that efforts to educate physicians should be directed more towards the diagnosis rather than the treatment of Lyme disease.

LYME DISEASE is the most common human vector-borne infection reported in the United States and, arguably, the second or third most important infectious disease to emerge in recent years. Maryland has ranked within the top 10 States in the annual incidence of the disease (*1*), and the shape of the epidemic curve in the State has paralleled that of the nation (*2,3*).

Antibiotic regimens have been advocated for the different stages of Lyme disease (*4–6*). However, because of the relative newness of this "emerging" infection and the prolonged followup required to assess treatment outcomes, therapeutic protocols are evolving. In addition, there is considerable debate regarding treatment of the many patients with chronic complaints not meeting the Centers for Disease Control and Prevention's (CDC's) case definition (*7*), particularly those with fibromyalgia and positive serological tests for Lyme disease (*8–11*).

We present data in this paper on the antibiotics

Table 1. Antibiotics used to treat 169 cases of Lyme disease having erythema migrans with, or without, arthritic, neurologic, or cardiac manifestations, Maryland 1991

Antibiotic	Route	Number	Percent
Doxycycline	PO	88	52.1
Tetracycline	PO	22	13.0
Amoxicillin	PO	25	14.8
Penicillin	PO	6	3.6
Erythromycin	PO	4	2.4
Cephalosporins	PO,IM	3	1.8
Ceftriaxone:			
Alone	IV	15	8.9
Plus doxycycline	PO	5	3.0
Doxycycline	IV	1	0.6
Total	. . .	169	100

NOTE: PO = oral, IV = intravenous, IM = intramuscular.

Table 2. Antibiotics used for treating 114 cases of Lyme disease having arthritic, neurologic, or cardiac manifestations without erythema migrans, Maryland 1991

Antibiotic	Route	Number	Percent
Doxycycline	PO	46	40.4
Tetracycline	PO	10	8.8
Amoxicillin	PO	11	9.6
Penicillin	PO	4	3.5
Erythromycin	PO	3	2.6
Cephalosporins	IM	1	0.9
Ceftriaxone:			
Alone	IV	23	20.2
Plus doxycycline	PO	9	7.9
Plus penicillin	IV	5	4.4
Doxycycline	IV	1	0.9
Penicillin	IV	1	0.9
Total	. . .	114	100

NOTE: PO = oral, IV = intravenous, IM = intramuscular.

selected by physicians in Maryland for treating Lyme disease to determine whether their treatment regimens differed from those recommended (*4–6*). Results of this survey served as baseline data and helped us to assess the need for an education module directed towards physicians in the State.

Methods

Starting in 1989, Lyme disease was included by the Maryland Department of Health and Mental Hygiene (DHMH) among the list of reportable diseases, and in 1990 information about antibiotics used in treatment was added to the case reporting form. Our survey reviewed all cases of Lyme disease reported to the DHMH with onset of symptoms in 1991. A total of 425 cases of possible Lyme disease came from two sources: (*a*) practicing physicians using the Maryland Confidential Morbidity Report and (*b*) diagnostic laboratories reporting positive results in serological tests.

Physicians reporting cases or ordering the diagnostic tests were mailed a Maryland Lyme Disease Case Report form which had questions regarding the case and the exposures, symptoms, and antibiotic therapy of the patients. If there was no response within 3 weeks (about half the cases) the physician's office was called and reminded to return the form.

Often information was obtained via the telephone. Incomplete case reports were also investigated by a telephone interview with the physician reporting the case. Fifty-two cases were excluded because the attending physician did not believe his or her patient had Lyme disease, or we could obtain no further information about the case.

These exclusions left 373 persons the reporting physician thought had Lyme disease. Ninety did not meet CDC's case definition (*7*) and were excluded from analysis. The reasons for exclusion were 32 had erythema migrans (EM) less than 5 centimeters (cm) in size; 23, flu-like symptoms and positive serology; 18, incomplete information; 9, arthralgia (that is, no reported joint swelling) and positive serology; and 8, only tick bite with or without positive serology. The 90 not meeting the case definition were treated, usually with oral doxycycline or tetracycline.

In 10 percent of the cases, the physician changed the antibiotics within the first week. About half the time this was because of the patient's intolerance or reaction to the first drug, and in about half the switch was to a chemotherapeutic regimen recommended for treating Lyme disease. The second therapeutic choice, which was invariabily the longest course of treatment, was the one used for our analysis. As noted in tables 1 and 2, some patients received complete courses of more than one antibiotic.

The results were analyzed with respect to symptomotology and other factors which might affect treatment choices. Differences in proportions among categorical variables were tested using chi-square analysis, and continuous variables were analyzed using the Student's *t*-test whenever appropriate.

Results

Of the 283 patients meeting CDC's criteria for Lyme disease, 169 (59.7 percent) were reported to have EM; 65 with and 104 without arthritic, neurologic, or cardiac manifestations (see figure). Of the remaining 114 (40.3 percent), 101 complained of arthritic, 16 of neurologic, and 4 of cardiac symptoms

without having the characteristic rash. (Although the physicians were to report only observed rashes, it was obvious that patient descriptions of prior EM influenced diagnostic decisions and were often included in the Lyme disease case report forms.)

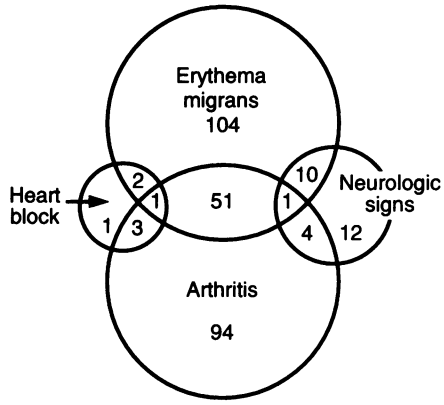
More than half the subjects (154 or 54.4 percent) had joint complaints. Ninety-four (33.2 percent) had only arthritis as a complaint, and arthritis occurred more frequently (odds ratio [OR] 1.6; confidence interval [CI] 0.9–2.7; $P=0.09$) in females (57 of 139 or 41.0 percent) than in males (44 of 144 or 30.6 percent). Neurological abnormalities were present in 27 subjects and included a combination of the following: 17 had facial palsy; 7, lymphocytic meningitis; 6, peripheral radiculitis; and 2, encephalitis. Eleven had neurological findings in either the presence of, or documented history of, EM while 16 did not. Five also had arthritis. The most common neurological presentation was facial palsy by itself; this condition was present in 16 (8 with EM and 1 each with concomitant arthritis or EM and arthritis). Seven patients had heart block with positive serological tests for Lyme disease. Three of these also had EM, or documented EM in the past, while four had concomitant arthritis (see figure).

The mean age of the subjects was 38.2 years, and the range was from 2 to 88. Lyme disease was more frequent (57, 20.1 percent) in those in the fifth (in their 40s) than in other decades. Slightly more than half, 144 (50.9 percent) of the subjects, were male.

The most frequently prescribed antibiotic for both the 169 patients with EM (table 1) and for the 114 presenting with arthritic, neurologic, or cardiac manifestations and no EM (table 2) was oral doxycycline. It or oral tetracycline were used to treat 109 (64.5 percent) of those with the rash, and 56 (49.1 percent) of those without EM. Amoxicillin and oral penicillin were used for treating 31 (18.3 percent) of those with EM and 15 (13.2 percent) of those without a rash. Twenty-eight (60.9 percent) of those receiving these two drugs were younger than 10 years. Doxycycline was used in only 1 of the 26 persons younger than 8 years. The most frequently used drug in this group (17, 65.4 percent) was oral amoxicillin.

Sixty patients (21.2 percent) received intravenous therapy. Ceftriaxone, with or without other antibiotics, was most frequently used (57, 95 percent). As expected, intravenous antibiotics were used more frequently (OR 3.7; CI 1.9–7.0; $P<0.001$) in those with arthritic, neurologic, and cardiac manifestations without EM (39, 34.2 percent) than in those with EM (21, 12.4 percent). In addition, intravenous therapy was more frequently used (OR 3.8; CI 1.3–11.2; $P=0.009$) in those with EM and arthritic, neurologic, and cardiac manifestations (14 of 65; 21.5 percent) than in those having EM only (7 of 104; 6.7 percent).

Venn diagram of the findings: 283 cases of Lyme disease meeting the Centers for Disease Control and Prevention's case definition and reported to the Maryland Department of Health and Mental Health in 1991



NOTE: Case reports often included a history of rash compatible with erythema migrans since the reporting physicians did not always differentiate this from observing the rash

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Intravenous antibiotics were more frequently used for patients having arthritis (41 of 154, 26.6 percent; OR 2.1; CI 1.1–4.0; $P=0.02$), neurological symptoms (13 of 27, 48.1 percent; OR 12.9; CI 3.9–43.8; $P<0.001$) and heart block (3 of 7, 42.9 percent; OR 2.9; CI 0.3–15.9; $P=0.34$) than for treating those having only EM (7 of 104, 6.7 percent).

In addition to variations in drugs and in route of administration, there was range in the dosage and length of therapy. The majority of treatment courses for all antibiotic regimens was from 2 to 3 weeks (table 3). Thirty patients (10.6 percent) were treated for less than 2 weeks while 51 patients (18.0 percent) were treated for longer than 3 weeks. The median length of therapy in all 283 cases was 20 days with 202 (71.4 percent) courses being given from 14 to 21 days, and 275 (97.2 percent) of courses being prescribed from 10 to 30 days. The most frequent (55

Table 3. Length of antibiotic therapy for 283 cases of Lyme disease, Maryland 1991

Antibiotic	Route	Total courses		Less than 14 days		Between 14 and 21 days		More than 21 days	
		Number	Percent	Number	Percent	Number	Percent	Number	Percent
Doxycycline	PO	134	47.3	8	6.0	98	73.1	28	20.9
Tetracycline	PO	32	11.3	5	15.6	23	71.9	4	12.5
Amoxicillin	PO	36	12.7	2	5.6	23	63.9	11	30.6
Penicillin	PO	10	3.5	2	20.0	7	70.0	1	10.0
Erythromycin	PO	7	2.5	2	28.6	3	42.9	2	28.6
Cephalosporins	PO,IM	4	1.4	3	75.0	0	. . .	1	25.0
Ceftriaxone:									
Alone	IV	38	13.4	1	2.6	34	89.5	3	7.9
Plus doxycycline	PO	14	4.9	4	28.6	9	64.3	1	7.1
Plus penicillin	IV	5	1.8	1	20.0	4	80.0	0	. . .
Doxycycline	IV	2	0.7	1	50.0	1	50.0	0	. . .
Penicillin	IV	1	0.4	1	100	0	. . .	0	. ..
Total	. . .	283	100	30	10.6	202	71.4	51	18.0

NOTE: PO= oral, IM = intramuscular, IV = intravenous.

' . . . efforts to educate physicians should be directed more towards the diagnosis rather than the treatment of Lyme disease.'

courses, 32.5 percent) length of treatment for EM was 21 days, and all but 3 of the 169 with EM were treated from 10 to 30 days.

The length of therapy for EM differed ($P=0.05$) between those with (mean, 19.9 days) and without (mean, 18.1 days) systemic symptoms. The mean length of therapy for the 114 patients presenting with arthritic, neurologic, or cardiac manifestations and no rash (20 days) was not significantly longer ($P>0.10$) than that of the 169 presenting with only EM (18.8 days). The most frequent schedule for the 34 patients (29.8 percent) with arthritic, neurologic, and cardiac manifestations without EM was also 21 days, but 22 (19.3 percent) were treated for 30 days, and 3 were treated longer.

Discussion

Our data provide evidence of the widespread adoption in Maryland of published treatment guidelines for Lyme disease (*4–6*). Oral doxycycline or tetracycline were the drugs most frequently prescribed and usually were given for 2 to 3 weeks. Amoxicillin or oral penicillin was substituted, with one exception, for children younger than 8 years, in whom tetracycline is contraindicated.

Physicians treated patients with arthritic, neurologic, or cardiac manifestations without the characteristic rash on an average of 2 days longer than they treated those presenting with only EM. Oral therapy was generally used in treating both EM and disseminated infection. However, one in seven with EM, mostly those with arthritic, neurologic, and cardiac findings, and one in three of those presenting with these more chronic lesions without EM, were treated intravenously. Seven patients with EM without arthritic, neurologic, or cardiac signs were treated with intravenous antibiotics, a regimen not generally recommended for treating uncomplicated EM (*4–6,14,15*). All seven had concomitant flu-like symptoms, which obviously influenced their physicians' therapeutic choices. Almost half of those with neurological symptomotology and heart block were treated intravenously, usually with ceftriaxone alone or in combination with other drugs.

It is generally accepted that 2 or 3 weeks of therapy is sufficient for treating early onset Lyme disease as manifested by EM (*4–6*). This almost always clears the rash and other symptoms and prevents more chronic manifestations. However, there is uncertainty regarding the choice and length of therapy for treating patients with joint or neurologic complaints, as well as controversy regarding treatment of patients with fibromyalgia and fatigue with positive serological tests for Lyme disease (*8–11*). Patients having the latter syndromes are seldom reported as cases of Lyme disease to the DHMH, and since they do not meet CDC's case definition for Lyme disease (*7*), are not included among our cases.

Whereas 10- to 30-day courses of oral doxycycline or amoxicillin are recommended for treating early infections (*6,12,13*), 30-day courses of these antibiotics

are the most frequently recommended therapy for Lyme arthritis. With the exception of patients with isolated facial palsy, those with neurological involvement are often treated with intravenous ceftriaxone or penicillin for 2 to 4 weeks (*14*). The basis for a longer course of treatment for chronic infections with complications is that *Borrelia burgdorferi* is a very slow grower with a 12-hour or longer generation time (*15*), and the bacteria is believed to persist in the tissues, particularly within the central nervous system.

The overdiagnosis and treatment of patients with chronic manifestations suggestive of Lyme disease is of major concern (*8–11*), since many of these patients are being treated with an expensive and potentially toxic regimen using intravenous ceftriaxone (*16*). Nine of the patients excluded from our report had only arthralgias and a positive serological test. Other causes of possible overdiagnosis and treatment included patients with small rashes, that is, having EM<5 cm in diameter (32 reports), and the inclusion of cases with only flu-like symptoms and positive serology (23 reports).

Most commericallly available serological tests are unreliable for diagnosing Lyme disease, although the most common problems differ with the stage of the infection, that is, a lack of sensitivity for detecting acute infections and poor specificity in those suspected of having chronic infections (*11*).

Another circumstance in which some physicians in the State overdiagnosed and treated Lyme disease was in patients who sought medical advice for tick bites (eight reports). Prophylactic treatment of persons having a tick bite has been documented to be inappropriate in an area with a far greater prevalence of Lyme disease than Maryland (*17*). The results of our investigation suggest that educational efforts for physicians in this State could be better directed towards improving diagnostic rather than therapeutic skills, at least until the ideal antibiotic regimens for the different stages and manifestations of Lyme disease have been determined.

References

1. Lyme disease-United States, 1991-1992. MMWR Morb Mortal Wkly Rep 43: 564–572, Aug. 12, 1994.
2. Mitchell, C. S., et al.: Lyme disease in Maryland: 1987–1990. Md Med J 41: 391–396 (1992).
3. Epidemiology and Disease Control Newsletter: Lyme disease in Maryland in 1992. Md Med J 42: 424–426 (1993).
4. Luft, B. J., et al.: A prospective on the treatment of Lyme borreliosis. Rev Infect Dis 11 (supp. 6): 1518–1525 (1989).
5. Rahn, D. W., and Malawista, S. E.: Lyme disease: recommendations for diagnosis and treatment. Ann Intern Med 114: 472–481 (1991).
6. Treatment of Lyme disease. Med Ltr 34: 95–97, Oct. 16, 1992.
7. Case definitions for public health surveillance. MMWR Morb Mortal Wkly Rep 39 (No. RR–13): 19–21, Oct. 19, 1990.
8. Sigal, L. H.: Summary of the first 100 patients seen at a Lyme disease referral center. Am J Med 88: 577–581 (1992).
9. Sigal, L. H., and Patella, S. J.: Lyme arthritis as the incorrect diagnosis in pediatric and adolescent fibromyalgia. Pediatrics 90: 523–528 (1992).
10. Lightfoot, R. W., et al.: Empiric parenteral antibiotic treatment of patients with fibromyalgia and fatigue and a positive serologic result for Lyme disease. A cost-effectiveness analysis. Ann Intern Med 119: 503–509 (1993).
11. Steere, A. C., et al.: The overdiagnosis of Lyme disease. JAMA 269: 1812–1816, Apr. 14, 1993.
12. Dattwyler, R. J., et al.: Amoxicillin plus probenecid versus doxycycline for treatment of Lyme borreliosis. Lancet Vol. 336: 1404–1406, Dec. 8, 1990.
13. Massarotti, E. M., et al.: Treatment of early Lyme disease. Am J Med 92: 396–403 (1992).
14. Dattwyler, R. J., Halperin, J. J., Volkman, D. J., and Luft, B. J.: Treatment of late Lyme borreliosis—randomized comparison of ceftriaxone and penicillin. Lancet 8596: 1191–1194, May 28, 1988.
15. Barbour, A. G., and Hayes, S. F.: Biology of *Borrelia* species. Microbiol Rev 50: 381–400 (1986).
16. Ceftriaxone-associated biliary complications of treatment of suspected disseminated Lyme disease—New Jersy, 1990–1992. MMWR Morb Mortal Wkly Rep 42: 39–42, Jan. 22, 1993.
17. Shapiro, E. D., et al.: A controlled trial of antimicrobial prophylaxis for Lyme disease after deer-tick bites. N Engl J Med 327: 1769–1973, Dec. 17, 1992.