Biliary Complications in the Treatment of Unsubstantiated Lyme Disease

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Treatment of unsubstantiated Lyme disease has led to serious complications in some cases. Two case-control studies, based on information in clinical records of patients discharged with a diagnosis of Lyme disease during 1990–1992, were conducted at a central New Jersey hospital. Twenty-five patients with biliary disease were identified, and 52 controls were selected from 1352 patients with suspected Lyme disease. Only 3% of 71 evaluatable subjects met the study criteria for disseminated Lyme disease. Patients with biliary disease were more likely than were antibiotic controls to have received ceftriaxone and more likely than ceftriaxone controls to have received a daily ceftriaxone dose ≥40 mg/kg and to be ≤18 years old. Fourteen of 25 biliary case-patients underwent cholecystectomy; all had histopathologic evidence of cholecystitis and 12 had gallstones. Thus, treatment of unsubstantiated diagnoses of Lyme disease is associated with biliary complications.

Lyme disease, a tickborne spirochetosis with protean clinical manifestations [1, 2], is the most commonly reported vectorborne infectious disease in the United States; nearly 50,000 patients with Lyme disease were reported nationwide during 1982–1992 [3].

In a recent community-based study of schoolchildren with suspected Lyme disease in central New Jersey, where the disease is endemic [4], a number of patients receiving in-home intravenous antimicrobial infusion therapy were hospitalized with biliary disease (CDC, unpublished data). A computerized search of statewide hospital discharge data found that 26% of all hospitalizations for a primary or secondary diagnosis of Lyme disease in the state in 1990–1991 were at one 500-bed central New Jersey teaching hospital (State of New Jersey Department of Health, unpublished data). Subsequently, we reviewed medical records at that hospital to identify risk factors for biliary disease in patients with a discharge diagnosis of Lyme disease and to determine whether they met criteria for a diagnosis of Lyme disease.

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Methods

Biliary case definition and determination. A biliary case was defined as any patient with cholecystitis, cholelithiasis, or a cholecystectomy within 90 days of treatment with any antimicrobial agent for suspected Lyme disease from 1 January 1990 through 11 November 1992 (the date retrospective chart review was begun). To identify patients with a discharge diagnosis of Lyme disease (International Classification of Diseases, 9th revision [ICD-9] code 088.81), a computerized search was made of medical records at the subject hospital. Case-patients with a diagnosis of both Lyme disease and biliary disease were identified by cross-referencing the Lyme disease code with codes for biliary disease (ICD-9 574.0-576.9) or cholecystectomy (ICD-9 51.22-51.23).

Epidemiologic study design. Next, we conducted two case-control studies. In the first, biliary case-patients were compared with randomly selected patients who had been treated for suspected Lyme disease with any antimicrobial agent but did not develop evidence of biliary disease (antibiotic controls). A second study, designed to examine dose-response, compared biliary case-patients with randomly selected patients who were treated for suspected Lyme disease with intravenous ceftriaxone but did not develop evidence of biliary disease (ceftriaxone controls). Potential subjects were excluded from the study if they had a history of biliary disease predating antimicrobial treatment for suspected Lyme disease. Hospital clinical records were reviewed for patient age, sex, ethnicity, weight, and medical history, including clinical symptoms, diagnostic evaluation, and treatment.

Substantiation of Lyme disease diagnosis. For each study subject, hospital records were reviewed to determine whether documented clinical and laboratory evidence substantiated a diagnosis of disseminated Lyme disease. A patient was considered to have a confirmed case of Lyme disease if there was at

Dermatologic:

- **Secondary (multiple) erythema migrans lesions**

Musculoskeletal:

- **Arthritis (brief attacks of swelling in ≥1 joint lasting hours to days, recurrent over months to years)**

Cardiac:

- **2° or 3° atrioventricular block**
- **Myocarditis or myopericarditis**

Neurologic:

- **Lymphocytic meningitis (headache and stiff neck with ≥5 lymphocytes per mm^3 of cerebrospinal fluid)**
- **Cranial neuritis**
- **Radiculoneuritis (radicular pain with documented motor weakness or sensory loss within a dermatomal distribution, or electromyographic evidence of a radiculoneuropathy)**
- **Peripheral neuritis (distal paresthesia with electromyographic evidence of an axonal polyneuropathy)**
- **Encephalopathy (memory deficit documented by abnormal results of neuropsychological tests*, and evidence of intrathecal production of antibodies to B. burgdorferi or elevated cerebrospinal fluid protein)**
- **Encephalomyelitis (spasticity and magnetic resonance imaging scan or computerized tomographic scan showing abnormalities in the brain or spinal cord, and evidence of intrathecal production of antibodies to B. burgdorferi)**

Ophthalmologic:

- **Keratitis (multiple focal opacities in varying levels of the corneal stroma)**

* Kaplan, et al. [9]

Figure 1. Clinical criteria for disseminated Lyme disease used in this study (based on published reports [1, 2, 5–9]).

least one documented objective clinical manifestation (figure 1) and at least one laboratory report indicating seropositivity for *Borrelia burgdorferi* by any technique, as interpreted by the laboratory that made the test. If the hospital record contained both seropositive and seronegative results, the patient was considered seropositive. If a patient's hospital record contained a clinical description meeting the study clinical criteria but no test results for antibodies to *B. burgdorferi*, no description of the clinical manifestations attributed to Lyme disease but a positive serologic test result, or neither a clinical description nor any serologic test results, the accuracy of the Lyme disease diagnosis was considered not assessable.

Statistical analysis. Biliary case-patients and control subjects were compared by use of Fisher's exact test for categorical variables and by Wilcoxon two-sample or Student's *t* tests for continuous variables. Potential risk factors for biliary disease were evaluated with adjusted (Mantel-Haenszel) odds ratios (ORs) and 95% confidence intervals (CIs). Pearson's correlation coefficient was calculated for two continuous variables.

Results

During the study period, the hospital under study admitted 1352 persons (1730 admissions; mean, 1.3 admissions/patient) for primary or secondary Lyme disease. These admissions were 2.6% of 67,579 total admissions. The cohort of 1352 patients had a median age of 16 years (range, 6 months to 86 years); 932 (69%) were female and 96% were non-Hispanic white. Twenty-five patients (1.8%) met the study case definition for gallbladder disease; 24 of these also had ultrasound evidence of gallbladder disease.

First case-control study. Biliary case-patients were more likely to have received ceftriaxone than were antibiotic controls (within 90 days of the occurrence of biliary disease for case-patients or ever for antibiotic controls) (25 of 25 vs. 15 of 26; $P < .001$, Fisher's exact test). Biliary case-patients were significantly younger than the 26 antibiotic controls (median age, 12 years; range, 3–40 vs. 15.5 years; range, 1–59; $P = .03$ by Wilcoxon two-sample test) and more likely to be female (21 of 25 vs. 14 of 26; $P = .03$, Fisher's exact test). All case-patients and antibiotic controls were non-Hispanic white.

Table 1 shows results of a stratified analysis. An age of ≤18 years was associated with biliary disease (OR, 8.2, adjusted for sex; 95% CI, 1.4–46.9).

Second case-control study. When we compared biliary

Table 1. Risk factors for biliary disease in two case-control Lyme disease studies in New Jersey.

	Age ≤18 years	Female	Ceftriaxone dose >40 mg/kg/day
Study 1			
Biliary case-patients, no. (%)	23/25 (92)	21/25 (84)	14/17 (82)
Antibiotic controls, no. (%)	15/26 (58)	14/26 (54)	—
OR*	8.2	4.1	—
95% confidence interval	1.4–46.9	0.99–17.3	—
Study 2			
Ceftriaxone controls, no. (%)	12/26 (46)	20/26 (77)	5/22 (23)
OR*	16.3	2.7	11.9†
95% confidence interval	2.9–90.8	0.5–13.0	2.6–54.2

* Adjusted Mantel-Haenszel summary odds ratios (ORs). OR for female sex is adjusted for age ≤18 years. OR for age ≤18 years is adjusted for sex. OR for age ≤18 years and sex could not be adjusted for ceftriaxone dose because of 0 cell values.

† OR for ceftriaxone dose adjusted for sex only because of correlation of age and ceftriaxone dose.

case-patients with ceftriaxone controls for whom we had daily ceftriaxone dose data, we found that case-patients were younger (median age, 11 years vs. 21.5; $P < .001$, Wilcoxon two-sample test), received a larger daily ceftriaxone dose (mean, 57 vs. 34 mg/kg; ranges, 27–96 vs. 16–59, respectively; $P < .001$, Student's t test), and were more likely to have received a daily dose of ceftriaxone >40 mg/kg (14 of 17 vs. 5 of 22; OR, 11.9, adjusted for sex; 95% CI, 2.6–54.2). Most older children, adolescents, and adult patients had received the same daily dose of ceftriaxone (2 g) regardless of body weight. Age and daily dose of ceftriaxone were inversely related (correlation by Pearson's $r = -0.65$; $P < .001$; figure 2); because of the strong correlation of these two variables, their independent effects on the risk of biliary disease could not be estimated.

Table 1 shows results of a stratified analysis. Again, an age of ≤18 years was associated with biliary disease (OR, 16.3, adjusted for sex; 95% CI, 2.9–90.8).

The cumulative dose of ceftriaxone could not be evaluated as a risk factor for biliary disease, because complete information on both dose and duration of treatment was available for too few subjects. For the 11 case-patients and 19 controls for whom complete information was available, the median duration of treatment was 23 days (range, 4–170). Seventeen other case-patients had previously been discharged from the subject hospital with physicians' orders to undergo "4 to 6 weeks" or longer of home intravenous infusion with ceftriaxone; however, complete information on duration of treatment was not available for these patients.

Management of biliary cases. Fourteen (56%) of the 25 biliary case-patients underwent laparoscopic cholecystectomy, all under general anesthesia. Their median age was 15 years (range, 7–40); 12 patients (86%) were ≤18 years of age, and 12 were female. Documented symptoms of biliary disease in the days or weeks preceding cholecystectomy included right upper quadrant abdominal pain (12 patients), nausea (5), and vomiting (4). No preoperative fever or rebound abdominal tenderness was documented. Preoperative pancreatitis was suspected in 1 patient. Results of preoperative gallbladder ultrasound studies were interpreted by the hospital radiology staff as showing evidence of cholelithiasis (without evidence of common bile duct stones) in 13 patients. In 5 cases (36%), the primary physician or surgical consultant attributed the biliary symptoms to ceftriaxone therapy. Twelve patients were switched perioperatively from ceftriaxone to another antibiotic (most commonly cefotaxime): 6 from a few days to a few weeks preoperatively and 6 postoperatively.

A histopathologic diagnosis of cholecystitis ("chronic" or "mild chronic") was recorded for all 14 patients. A pathologic diagnosis of cholelithiasis was made in 12 cases (86%); gallbladder calculi, usually greenish, ranged from 1 to many with diameters of 2–10 mm. No stones were submitted for chemical analysis. No patients had documented common duct stones.

Biliary disease in 11 (44%) of 25 biliary case-patients was managed nonsurgically. After 10 patients were changed from ceftriaxone to another antibiotic (most commonly cefotaxime), biliary symptoms were thought to have resolved.

Lyme disease: clinical manifestations and serologic results. For the 77 biliary case-patients and control subjects in the two studies, symptoms attributed to Lyme disease began a median of 2 years (range, 6 weeks to 8 years) before the most recent hospital admission. Symptoms attributed to Lyme disease included arthralgia (78% of subjects), headache (72%), fatigue (47%), difficulty with concentration or memory (22%), myalgia (19%), fever (17%), and blurred vision (17%). Only 5 subjects (6%) had physician-observed erythema migrans documented.

Seven (10%) of 71 study subjects whose hospital records contained a description of the clinical manifestations attributed to Lyme disease met the study clinical criteria for disseminated Lyme disease. These included 3 (13%) of 24 biliary case-patients and 4 (9%) of 47 controls. Documented objective manifestations of Lyme disease in these 7 patients included arthritis (3), secondary erythema migrans (2), facial palsy (1), and optic neuritis (1). Twenty-two (36%) of 61 patients whose records showed at least 1 test for antibodies to *B. burgdorferi* met the study serologic criteria for disseminated Lyme disease. These included 9 (41%) of 22 biliary case-patients and 13 (33%) of 39 controls. Of these 61 subjects, 8 (13%) had a positive *B. burgdorferi* antibody test documented, 14 (23%) had both positive and negative results, and 39 (64%) had only negative results documented. Serologic test methods used in a given case, either singly or in combination, were EIAs, immunofluorescent assays, and Western im-

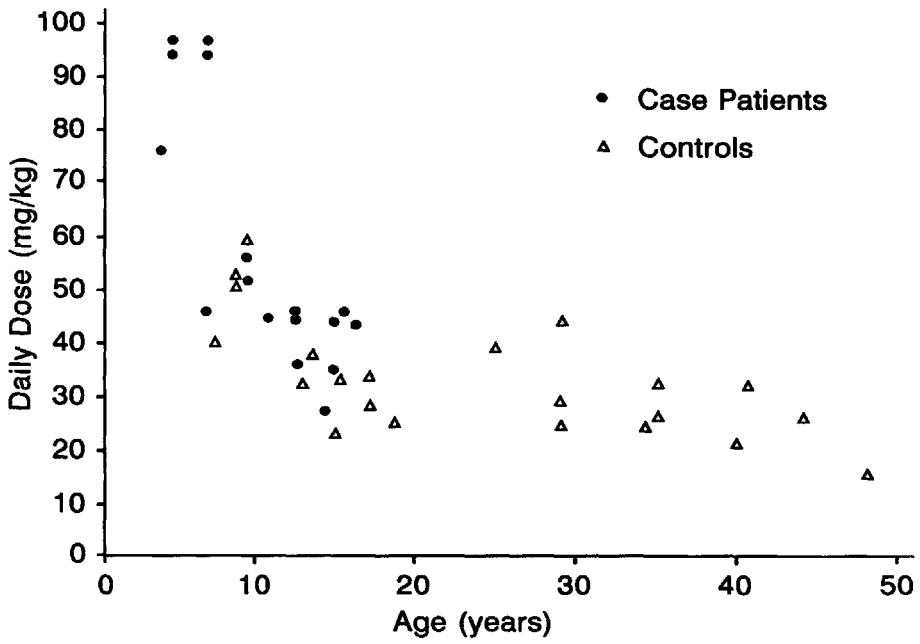

Figure 2. Scatterplot of age vs. daily ceftriaxone dose in case-patients and ceftriaxone controls in second case-control study.

munoblots. Of the 71 evaluatable study subjects, 2 (3%) met both the clinical and laboratory study criteria for disseminated Lyme disease. The other 6 subjects were not evaluatable.

The median number of hospitalizations of all 77 study subjects for treatment of suspected Lyme disease was 2 (range, 1–6). The median length of stay per admission was 8 days (range, 1–81) for biliary case-patients and 6 days (range, 1–42) for controls. Each study subject had received a median of 3 (range, 1–9) courses of antimicrobial agents (oral, intravenous, or both) for treatment of suspected Lyme disease. In addition to ceftriaxone, the most commonly prescribed antimicrobials included amoxicillin, ampicillin, cefixime, cefotaxime, doxycycline, and penicillin.

Discussion

During 1990–1992, numerous persons were admitted to one central New Jersey hospital for treatment of suspected Lyme disease. At that hospital, the admission rate for a primary or secondary diagnosis of Lyme disease (2.6% of 67,579 admissions) was >20-fold higher than the combined rate at all other New Jersey hospitals in the same period (4846 of $4.07 \times 10^6 = 0.1\%$; $P < .001$, χ^2 test; State of New Jersey Department of Health, unpublished data). The biliary case-patients and control subjects we studied were mostly adolescent and preadolescent girls admitted for initiation of intravenous antimicrobials or for management of complications of treatment. Their demographic profile was similar to the overall population of hospitalized Lyme disease patients from whom they were selected but differed from nationwide [3] and statewide New Jersey [10] Lyme disease cases where the male to female ratio is ~1:1 and the largest proportion of cases occurs in those 35–60 years old. Studies in New Jersey and elsewhere have shown that patients misdiagnosed with late-stage Lyme disease are most likely to be young girls [11–13].

The recommended treatment of disseminated Lyme disease is 3–4 weeks of an oral or intravenous antimicrobial agent, most commonly ceftriaxone [1, 14–17]. Many subjects in the current study had received prolonged (>4 weeks) and repeated courses of antimicrobial agents for suspected disseminated Lyme disease. Treatment was commonly begun in the hospital and followed by several weeks of in-home intravenous infusion therapy. Prolonged antimicrobial treatment of disseminated Lyme disease is controversial, and controlled trials of its efficacy have not been published [17]. Not uncommonly, patients receiving this type of treatment have nonspecific symptoms suggestive of chronic fatigue or fibromyalgia and a positive serologic test for Lyme disease. A recent study indicates that risks and costs of treatment in these circumstances are likely to exceed benefits [18].

Systematic studies of the complications of treating disseminated Lyme disease have not been reported, although individual cases have been described [19, 20]. Our study was prompted by the finding that many central New Jersey children being treated for Lyme disease at home with intravenous antimicrobials required hospitalizations for biliary disease and bloodstream infections (CDC, unpublished data). It is remarkable that we identified 25 patients hospitalized for treatment of suspected Lyme disease during a 34-month period who developed cholecystitis or cholelithiasis and that 14 of these patients, most of them children, underwent laparoscopic cholecystectomy.

All 77 subjects in our case-control studies were treated ≥6 weeks for suspected disseminated Lyme disease, despite a

lack of both seropositivity and documented objective clinical manifestations in all but a few. Although routinely available serologic tests for Lyme disease often lack accuracy and reproducibility [21, 22], most patients with disseminated Lyme disease have antibodies to *B. burgdorferi* [5, 7, 8, 23] and most have objective signs of arthritis or neurologic disease not accounted for by other causes [1, 2, 7–9]. The lack of objective evidence of Lyme disease for most patients in the current study may have been due to incomplete hospital records or to misdiagnosis [11–13, 19, 20, 24].

Our case-control studies showed that biliary disease was strongly associated with administration of ceftriaxone within 90 days of the onset of symptoms. Biliary case-patients were more likely than controls to have received both a higher average daily dose of ceftriaxone and a daily dose (>40 mg/kg of body weight), which suggests a dose threshold for biliary complications. Biliary precipitation of ceftriaxone as sludge was first observed in animal studies [25]. The first occurrence in a human was reported in 1986 [26], and sporadic cases and several case-series have subsequently been reported [27–38]. Nevertheless, ceftriaxone-induced biliary sludge and its frequency are probably not widely recognized; the manufacturer notes only that it is one of a number of "rarely observed" complications that occur in <0.1% of patients treated with the drug [39]. The daily doses received by case-patients in the current study and in other studies of ceftriaxone precipitation [26–38] are within the manufacturer's recommended ranges of 1–4 g for adults and 50–100 mg/kg of body weight (not to exceed 4 g/day) for children [39].

Most reports recommend cessation of ceftriaxone for patients who develop biliary symptoms while receiving the drug, since cessation usually leads to spontaneous resolution of signs and symptoms [27–33, 35, 38]. In rare cases of symptomatic common bile duct stones related to ceftriaxone administration, endoscopic sphincterotomy and stone extraction may be indicated [27]. In the current study, the majority of patients with evidence of cholelithiasis were managed surgically. Laparoscopic cholecystectomy is popular and may be associated with less morbidity than laparotomy, but it is not a benign procedure. Intraoperative bile duct injuries have been reported in ~0.6% of laparoscopic cholecystectomies, and recognition of such injuries may be delayed [40]. Rare deaths have been reported [41].

The gallbladders of all 14 patients in our study who underwent cholecystectomy showed pathologic evidence of cholecystitis, and 12 (86%) contained discrete stones. These results were unexpected; in combined results of previous studies only 1 (11%) of 9 gallbladders removed as a result of ceftriaxone-associated biliary disease had evidence of cholecystitis on histopathologic examination and only 2 (22%) of 9 gallbladders contained frank stones [28, 30, 34]. The manufacturer of ceftriaxone does not list gallstones as an adverse reaction [39].

We conclude that an unsubstantiated diagnosis of Lyme disease is associated with biliary complications of treatment. Physicians who may encounter patients with Lyme disease should be familiar with current recommendations for diagnosis and treatment of this relatively new and emerging disease [1, 14–17] and know how to minimize the risk of potential treatment complications.

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