

Incidence and Patterns of Extended-Course Antibiotic Therapy in Patients Evaluated for Lyme Disease

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Background. Most patients with Lyme disease (LD) can be treated effectively with 2–4 weeks of antibiotics. The Infectious Disease Society of America guidelines do not currently recommend extended treatment even in patients with persistent symptoms.

Methods. To estimate the incidence of extended use of antibiotics in patients evaluated for LD, we retrospectively analyzed claims from a nationwide US health insurance plan in 14 high-prevalence states over 2 periods: 2004–2006 and 2010–2012.

Results. As measured by payer claims, the incidence of extended antibiotic therapy among patients evaluated for LD was higher in 2010–2012 (14.72 per 100 000 person-years; n = 684) than in 2004–2006 (9.94 per 100 000 person-years; n = 394) ($P < .001$). Among these patients, 48.8% were treated with ≥ 2 antibiotics in 2010–2012 and 29.9% in 2004–2006 ($P < .001$). In each study period, a distinct small group of providers (roughly 3%–4%) made the diagnosis in $>20\%$ of the patients who were evaluated for LD and prescribed extended antibiotic treatment.

Conclusions. Insurance claims data suggest that the use of extended courses of antibiotics and multiple antibiotics in the treatment of LD has increased in recent years.

Keywords. Lyme disease; insurance claim review; inappropriate prescribing; antibiotic use.

Lyme disease (LD), the most common tick-borne disease in the United States [1–3], is usually diagnosed based on erythema migrans and a history or risk of tick bite, which may be supported by a serologic test [4]. Early LD can be treated effectively with 2 weeks and late LD with 4 weeks of antibiotics [5,6]. After standard treatment with antibiotics, about 10%–20% of patients report persistent symptoms, such as fatigue, widespread musculoskeletal or joint pain, cognitive difficulties, or mood and memory disturbances [7–9]. These symptoms are nonspecific and are also prevalent in the general population [10, 11].

Persistence of symptoms for ≥ 6 months—known as posttreatment LD syndrome [5, 12]—is both a diagnostic and a management problem. Whether or not to use antibiotic treatment for patients with apparent persistent LD symptoms or to prevent them is a concern among patient communities, expressed in traditional and social media [13–15]. Although the pathogenic mechanisms underlying persistent symptoms remain unclear [16–23], concern over persistence of *Borrelia burgdorferi* leads some physicians to treat patients with extended courses of antibiotics [24, 25], despite multiple studies demonstrating that extended antibiotic therapy may be harmful [26] and provide no meaningful benefit [5, 19–23, 27]. Prolonged antibiotics are not recommended by the Infectious Disease Society of America (IDSA) for either early or late LD or posttreatment LD symptoms [5]. We sought to define the incidence and patterns of extended use of antibiotics in patients evaluated for LD (EAPLD) in 14 states with high LD prevalence.

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METHODS

Study Population and Data

We performed a population-based retrospective cohort study using insurance claims from a nationwide employer-provided health insurance plan in the United States. Data sets were constructed for 2 comparison time periods: 2004–2006 and 2010–2012. Our study population consists of all individuals from 14 states with high-prevalence of LD (Connecticut, Delaware, Maine, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont, Virginia, and Wisconsin) [28] who enrolled in the health insurance plan in ≥ 1 study period. Because zip codes may be outdated or overwritten by a new address, each individual's location was approximated using the zip code of the provider who made the first LD diagnosis. Fortunately, the 2004–2006 data was obtained at the time and the addresses had not been overwritten since then. Furthermore, the rate of EAPLD cases in each state was very similar whether the location was determined by the provider or the member's zip code ($r = 0.98$; $P < .001$).

Each encounter was coded with up to 4 *International Classification of Diseases, Ninth Revision* (ICD-9) codes. Prescription drugs were reported by date, National Drug Code, and quantity dispensed (in days). Laboratory orders were coded with Current Procedural Terminology code. Each visit had an associated provider zip code. Following established practices [29], we merged 2 visits with the same diagnostic codes into a "condition era" if the time interval between them was < 30 days (ie, using a 30-day persistence window). Similarly, if a new prescription was refilled within 30 days of the end date of a previous prescription, the 2 prescriptions were merged into a single "drug era" and treated as continuous therapy based on a 30-day persistence window [30]. The Boston Children's Hospital

Institutional Review Board approved the study, granting a waiver of consent.

Case Identification

Patients were initially included in the cohort of newly diagnosed patients with LD if they had ≥ 1 LD diagnostic code (ICD-9 code, 088.81) in the principal diagnosis field of a claim between 1 January 2004 and 31 December 2006 or between 1 January 2010 and 31 December 2012. Any patient having LD ICD-9 codes in the year prior to the start date of each study period was excluded. Furthermore, any patient having LD ICD-9 codes in both periods was counted only in 2004–2006.

We adapted a LD case definition developed based on claims data [31]. Cases were required to have orders for serologic testing for *B. burgdorferi* (Current Procedural Terminology code, 86618 and 86617 for enzyme immunoassay and Western immunoblot, respectively), and ≥ 1 serologic test order was required within 90 days before or after the any LD condition eras. We defined treatment for LD as a ≥ 2 -week course of one of the antibiotics recommended for the treatment of LD by the IDSA (doxycycline, amoxicillin, cefuroxime axetil, ceftriaxone, cefotaxime, penicillin G, and azithromycin, clarithromycin, and erythromycin for adult patients intolerant of amoxicillin, doxycycline, and cefuroxime axetil) [5], provided that treatment began within 30 days before or after the any LD condition eras. Patients evaluated for LD (PLD) require ≥ 1 validated treatment order. The EAPLD definition requires the antibiotic course ordered to be ≥ 5 weeks. In summary, the EAPLD case definition requires ≥ 1 LD ICD-9 code, ≥ 1 LD serologic testing order, and antibiotic therapy for ≥ 5 weeks. The PLD definition is similar, but the length of antibiotic therapy required is ≥ 2 weeks.

Table 1. Demographic Characteristics of Patients Evaluated for Lyme Disease and Given Extended Antibiotic Therapy in 2004–2006 and 2010–2012

Characteristic	No. (%)			
	Insured Individuals		Patients Evaluated for LD and Given Extended Antibiotic Therapy	
	2004–2006	2010–2012	2004–2006	2010–2012
Patient	1 694 618	1 943 588	394	684
Sex				
Male	777 373 (45.9)	902 896 (46.4)	171 (43.4)	261 (38.2)
Female	917 245 (54.1)	1 040 692 (53.5)	223 (56.6)	423 (61.8)
Age, y				
0–14	216 503 (12.8)	250 705 (12.9)	35 (8.9)	69 (10.1)
15–49	609 400 (36.0)	717 202 (36.9)	174 (44.2)	323 (47.2)
≥ 50	868 715 (51.3)	975 681 (50.2)	185 (47.0)	292 (42.7)

Abbreviation: LD, Lyme disease.

Statistical Analysis

Significance was tested with a Z statistic for comparison of rates and with Student *t* test for comparison of means. All analyses were performed using R software (version 3.1.0, R Foundation for Statistical Computing, <http://www.r-project.org/>). All statistical tests were 2 sided with an α error level of .05.

RESULTS

Incidence Rate of EAPLD

In the 2004–2006 period, 1 694 618 insured individuals (3 965 709 person-years) resided in the 14 states with high-prevalence of LD. Of these, 394 individuals met our full inclusion criteria for EAPLD. In the 2010–2012 period, 1 943 588 insured individuals (4 647 609 person-years) lived in the 14 states. Of these, 684 met the EAPLD criteria. The demographic characteristics for EAPLD cases in the 2 study periods are described in Table 1. In both study periods, these patients exhibited a strong female predominance. The distributions by month of diagnosis for PLD and EAPLD cases are shown in Figure 1. The percentages of PLD cases diagnosed in the summer months (May–August), when incident LD is most common, were 64.6% in 2004–2006 and 59.3% in 2010–2012, and the equivalent percentages for EAPLD were 52.8% and 49.6%, respectively. EAPLD cases were more likely to be diagnosed outside summer months in both study periods ($P < .001$). In the 2004–2006 period, 25 patients in the EAPLD category were hospitalized within 30 days of an outpatient LD diagnosis, with 9 hospitalizations clearly

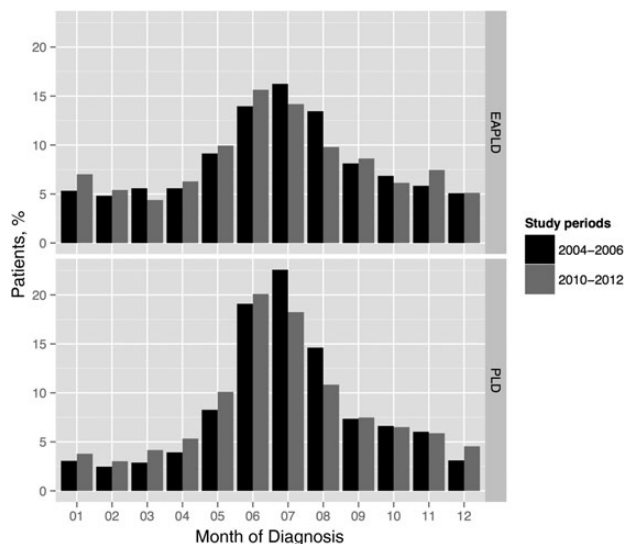


Figure 1. Distribution of diagnosis dates (by month, represented numerically) for patients evaluated for Lyme disease (PLD) and extended use of antibiotics in patients evaluated for Lyme disease (EAPLD) in 2004–2006 and 2010–2012.

associated with a diagnosis of LD. In the 2010–2012 period, 39 patients in the EAPLD category were hospitalized, with 24 of the hospitalizations associated with a diagnosis of LD.

The mean annual incidence rates of EAPLD cases estimated from claims data in 2010–2012 (14.72 cases per 100 000 per year) was higher than in 2004–2006 (9.94 cases per 100 000 per year) ($P < .001$). For comparison, the rates of PLD from the same data set for the same periods are also estimated. Among PLD, the percentages of EAPLD cases were 18.0% and 18.6% in 2004–2006 and 2010–2012, respectively.

Providers of EAPLD

Respectively, there were 279 and 488 providers for EAPLD cases in 2004–2006 and 2010–2012. The geographic distributions of these cases based on provider location are shown in Figure 2. Figure 3 shows the cumulative percentage of EAPLD cases by number of providers. Eleven of 279 and 16 of 488 providers treated 20.8% and 20.0% of EAPLD cases in 2004–2006 and 2010–2012, respectively.

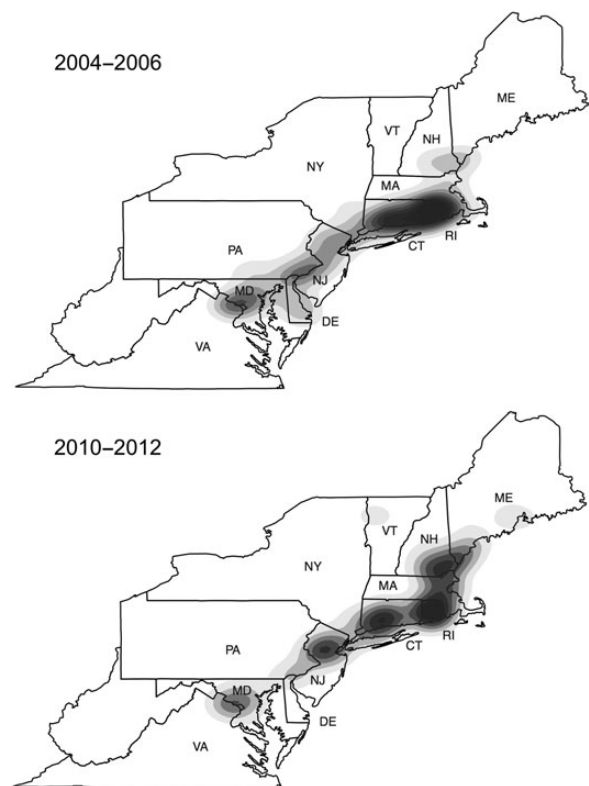


Figure 2. Geographic distribution of extended use of antibiotics in patients evaluated for Lyme disease (EAPLD) based on location in 2004–2006 and 2010–2012. The distribution graph is made by 2-dimensional kernel density estimations based on the number of cases diagnosed by each provider and the provider's zip code, adjusted by the number of participants from each state in our data set. (Wisconsin and Minnesota are not mapped because these states had <3% of all EAPLD cases in the 2 study periods.)

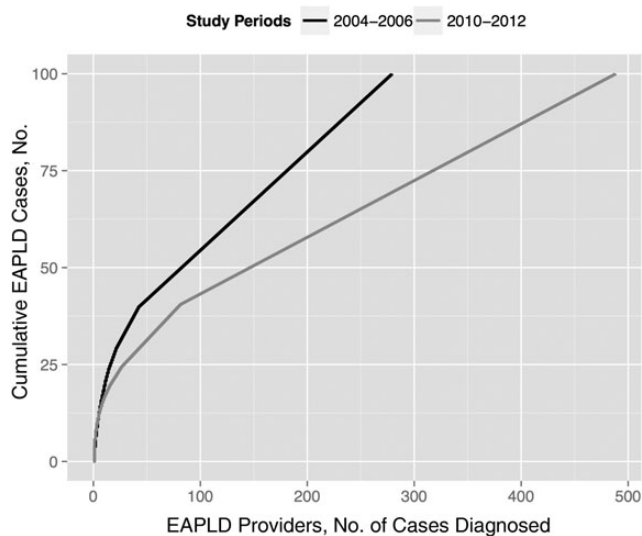


Figure 3. Cumulative percentages for extended use of antibiotics in patients evaluated for Lyme disease (EAPLD) in 2004–2006 and 2010–2012, plotted against prescribing providers, ordered by the number of EAPLD cases diagnosed. Eleven of 279 providers treated 20.8% of EAPLD cases in 2004–2006, and 16 of 488 providers treated 20.0% of cases in 2010–2012.

Extended-Course Antibiotics Used in PLD

Antibiotic therapy choices are shown in Table 2. For patients with >1 antibiotic course, we selected the longest course for analysis. Doxycycline was used in 74.1% and 62.4% of the longest courses of antibiotic therapy in 2004–2006 and 2010–2012, respectively. The percentage for azithromycin in the longest courses increased from 0.5% to 11.5% over the 2 study periods. Of patients receiving azithromycin in 2010–2012, 53.8% were also treated with first-line oral regimens (amoxicillin, doxycycline, and cefuroxime axetil). Between the 2 study periods, the average numbers of exposure days based on claim prescriptions were similar, but the average number of refills was higher

in 2010–2012 than in 2004–2006 ($P < .05$). The percentages of patients treated with combined antibiotics at the same time and of those switching to a different antibiotic therapy were both higher in 2010–2012 than in 2004–2006 ($P < .001$).

Providers accounting individually for treatment of >1% of EAPLD cases diagnosed more such cases, but they did not differ from their peers in their overall prescribing, as measured by the average number of antibiotic exposure days, number of refills in the longest drug era, and prescribing of multiple antibiotics (Table 3). Although doxycycline is the most common antibiotic used for LD therapy, these providers prescribed more cefuroxime axetil for EAPLD in 2004–2006 ($P < .001$) and more azithromycin in 2010–2012 ($P < .001$).

DISCUSSION

We identified patients who had been evaluated for LD and were treated with ≥ 5 weeks of antibiotics, finding a consistent 18% rate of EAPLD among such patients across the 2 study periods. However, the incidence of both PLD and EAPLD increased over time, as did the number of prescription refills for EAPLD and the percentage of EAPLD cases treated with ≥ 2 antibiotics.

Concerns about the risk of prolonged symptoms after recommended treatment may be driving a trend toward more prolonged and intensive therapy of LD. About half of New Englanders surveyed thought that prolonged treatment was sometimes useful and about a quarter thought it was always useful [14]. Our comparison of claims data from 2004–2006 and 2010–2012 is consistent with a trend toward use of longer courses and multiple agents. Posttreatment LD syndrome, sometimes called chronic LD, is a condition that seems to follow LD, especially when the diagnosis is delayed or the treatment inadequate [32]. Although multiple studies have concluded that extended antibiotic therapy provides no meaningful benefit [19–23], some patients continue antibiotics beyond 5 weeks for

Table 2. Extended-Course Antibiotic Regimens in Patients Evaluated for Lyme Disease in 2004–2006 and 2010–2012

Regimen Details	2004–2006	2010–2012	P Value
Most common antibiotic ^a	Doxycycline hyclate (74.1%); amoxicillin (15.7%)	Doxycycline hyclate (62.4%); amoxicillin (12.0%)	...
Exposure duration, d ^a			
Mean (SD)	80.0 (53.5)	85.7 (59.9)	.11
IQR	44	52	
Range (Min–Max)	370 (35–405)	369 (35–404)	
Refills, Mean (SD), No. ^a	2.7 (1.4)	3.0 (2.3)	<.05
Switch to different antibiotic, No. (%)	105 (26.6)	295 (43.1)	<.001
Combination antibiotic therapy, No. (%)	22 (5.6)	123 (18.0)	<.001
Only 1 prescription, No. (%)	35 (8.9)	60 (8.8)	.95

Abbreviations: IQR, interquartile range; SD, standard deviation.

^a If patients received >1 antibiotic course, we selected the longest course for analysis.

Table 3. Extended-Course Antibiotic Regimens in Patients Evaluated for Lyme Disease in 2004–2006 and 2010–2012, Comparing Providers Accounting for >1% of the Extended Use of Antibiotics in Patients Evaluated for Lyme Disease Cases Individually With Other Providers

Regimen Details	2004–2006			2010–2012		
	>1% EAPLD Providers	Other Providers	<i>P</i> Value	>1% EAPLD Providers	Other Providers	<i>P</i> Value
Exposure duration, Mean (SD) (IQR), d ^a	88.2 (53.7) [42.8]	77.5 (52.9) [42.2]	.10	93.9 (57.7) [73.2]	84.4 (60.2) [47.0]	.15
Refills, Mean (SD), No. ^a	2.8 (1.5)	2.6 (1.4)	.27	3.3 (1.9)	2.9 (2.3)	.13
Antibiotics, No. (%) ^a						
Doxycycline	51 (54.3)	241 (80.3)	<.001	43 (46.7)	384 (64.9)	<.001
Amoxicillin	21 (22.3)	41 (13.7)	<.05	11 (12.0)	57 (9.6)	<.01
Azithromycin	1 (1.1)	1 (0.3)	.38	22 (23.9)	57 (9.6)	<.001
Cefuroxime	18 (19.1)	15 (5.0)	<.001	10 (10.9)	50 (8.4)	.44
Antibiotic switch, No. (%)	26 (27.7)	79 (26.3)	.80	45 (48.9)	250 (42.2)	.23
Combination antibiotic therapy, No. (%)	5 (5.3)	17 (5.7)	.90	18 (19.6)	105 (17.7)	.67

Abbreviations: IQR, Interquartile range; SD, standard deviation.

^a If patients received >1 antibiotic course, we selected the longest course for analysis.

persistent symptoms or perceived need. When patients seek information online [33], they are likely to find advocacy for prolonged antibiotics. Cooper [15] found that of 19 Web sites analyzed, 9 posted unproven statements about posttreatment LD syndrome.

The cause of posttreatment LD syndrome has not been identified, nor has it been established that the syndrome represents only a single condition [34, 35], and experts disagree on the precise definition. A Connecticut survey found that only 2.1% of physicians were diagnosing and treating posttreatment LD syndrome, and 48% of physicians remained undecided about its existence [36]. Interestingly, we found that relatively few providers account for a large proportion of treatment for EAPLD, consistent with the general impression that certain providers use extended courses of antibiotics.

The antibiotic regimens used for EAPLD cases differed between the 2 study periods. Although macrolides are less effective than the first-line oral regimens [37, 38] and not recommended as first-line therapy for early LD [5], the use of azithromycin increased in 2010–2012. Providers accounting individually for >1% of EAPLD cases were more likely to prescribe antibiotics such as cefuroxime axetil in 2004–2006, and azithromycin in 2010–2012. More than half of EAPLD cases treated with azithromycin had also received a shorter, probably ineffective, course of first-line oral regimens, suggesting that physicians may have tried to use recommended antibiotics without satisfactory results.

Some factors may lead to an overestimation of EAPLD. Even though claims data have proved to be a useful source of disease identification [39, 40], coding can be inaccurate. Moreover, because claims data reveal tests ordered but do not generally include test results, some patients with negative results may be included as cases. Furthermore, patients with LD diagnosed by alternative methods—for example, Western blot analysis

performed outside reference laboratories—have a very high false-positive rate and share many characteristics with patients who have chronic fatigue syndrome [35]. However, we have minimized these effects by using a strict case definition that combined test order, LD diagnostic code, and antibiotic treatment as criteria and further stipulated that treatment began between 30 days before and 30 days after the LD condition eras.

Other factors may cause an underestimation of EAPLD rates. LD can be diagnosed clinically in patients with erythema migrans who live in or have traveled to endemic areas without an order for serologic testing [5]. Patients with early LD who were not tested or had a test not approved by the Food and Drug Administration would not be identified as having a test ordered and would not meet the PLD case definition. In the first and second study periods respectively, 118 and 243 potential EAPLD cases did not meet our case definition because of the lack of a test order and therefore were not included. Furthermore, because there was no inpatient medication data available in our data set, EAPLD cases treated in inpatient settings would not be identified.

About 6% of patients meeting EAPLD criteria were hospitalized within 30 days of an outpatient LD diagnosis in both study periods. About half of hospitalizations were clearly associated with an LD diagnosis, but only 0.4% of patients meeting EAPLD criteria in our data set had claims for intravenous antibiotics. This may be due to limited insurance coverage for EAPLD, requiring out-of-pocket payment; claims data set used was obtained from a payer with a prior approval policy for prolonged antibiotics.

CONCLUSIONS

The highly complete medication dispensing records found in insurance claims data offer insight into prescribing patterns of

antibiotics for treatment of LD, augmenting the understanding of treatment patterns gleaned from conventional surveillance systems. Despite consensus on the duration of therapy, including explicit IDSA guidelines for the treatment of LD, there remains considerable variation in therapy prescribed, with a small group of providers accounting for a substantial fraction of PLD receiving extended antibiotic courses. Some of the variation in treatment patterns is probably generated by a belief that longer courses of treatment are better at preventing long-term consequences of LD, some may arise from a belief that the persistence of LD symptoms requires more extended therapy, and some may be related to patient fear of the possible long-term consequences of undertreated LD.

Notes

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