

Failure of Treatment With Cephalexin for Lyme Disease

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Context: Lyme disease typically presents with a skin lesion called erythema migrans (EM), which though often distinctive in appearance may be confused with cellulitis. The first-generation cephalosporin, cephalexin monohydrate, is effective for treating bacterial cellulitis but has not been recommended or studied for treating Lyme disease because of poor in vitro activity.

Objective: To describe the outcome of patients with EM who were treated with cephalexin.

Patients and Methods: Patients presenting with EM to the Lyme Disease Diagnostic Center in Westchester, NY (May 1992-September 1997). A 2-mm punch biopsy specimen of the leading edge of the EM lesion and/or blood was cultured for *Borrelia burgdorferi*.

Results: Eleven (2.8%) of 393 study patients had been

initially treated with cephalexin prior to our evaluation; 9 (82%) were originally diagnosed with cellulitis. Cephalexin was administered for 8.6 days (range, 2-21 days) prior to presentation. All 11 patients had clinical evidence of disease progression, including 8 whose rash enlarged, 2 who developed seventh-nerve palsy (1 with new EM lesions), and 1 who developed new EM lesions. *Borrelia burgdorferi* grew in cultures from 5 patients despite a mean of 9.8 days of treatment with cephalexin (range, 5-21 days).

Conclusion: Cephalexin should not be used to treat early Lyme disease and should be prescribed with caution during the summer months for patients believed to have cellulitis in locations where Lyme disease is endemic.

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CEPHALEXIN is an oral first-generation cephalosporin antibiotic with good in vitro activity against *Streptococcus pyogenes*

and many strains of *Staphylococcus aureus*.¹ In addition, cephalexin is relatively inexpensive and well tolerated. For these reasons, it is often prescribed for the treatment of patients with bacterial cellulitis.²

Borrelia burgdorferi infection of the skin in early Lyme disease is associated with a skin lesion called erythema migrans (EM). When central clearing or a targetlike appearance is present, the lesion is unlikely to be confused with cellulitis caused by *S pyogenes* or *S aureus*. However, misdiagnosis is possible for patients with EM who do not present with classic features.^{3,4} Such patients may be inadvertently treated with cephalexin, an

antimicrobial not recommended for this indication. We describe 11 such patients with EM who were initially treated with cephalexin.

RESULTS

PATIENT CHARACTERISTICS

Between May 1992, and September 1997, 393 patients with EM entered a Lyme disease research protocol. Eleven patients (2.8%) with EM were taking or had completed a course of cephalexin at the time of presentation. The clinical characteristics of these 11 patients are summarized in **Table 1**. In 9 (82%) of 11 patients, the prescribing clinician had diagnosed cellulitis. Eight of these 9 patients presented with atypical features of EM, which presumably led to this diagnosis. Six had

PATIENTS, MATERIALS, AND METHODS

PATIENT ENROLLMENT AND *B BURGdorFERI* ANTIBODY TESTING

Patients seen at the walk-in Lyme Disease Diagnostic Center, Westchester Medical Center, Westchester, NY, between May 1, 1992, and September 30, 1997, with a rash consistent with EM were evaluated for entry into a diagnostic research protocol involving the cultivation of *B burgdorferi* from skin biopsy specimens or blood. This protocol was approved by the New York Medical College Institutional Review Board for research on human subjects. Those enrolled, after giving written informed consent, underwent a comprehensive history and physical examination. Blood was obtained at baseline and 10 to 20 days later for a polyvalent enzyme-linked immunosorbent assay (ELISA) to measure antibodies to *B burgdorferi* (Whittaker STAT ELISA kit; Whittaker Bioproducts Inc, Walkersville, Md). Samples were tested and interpreted according to the manufacturer's directions.

B BURGdorFERI CULTURE SPECIMENS

A 2-mm punch biopsy specimen was obtained from the leading edge of the EM lesion and placed into "incomplete" Barbour-Stoenner-Kelly (BSK) media.⁵ In certain patients, heparinized whole blood, serum, or plasma was also obtained for culture of *B burgdorferi*. Within 2 to 3 hours of collection, both skin- and blood-derived specimens were placed into BSK medium, incubated, and inspected for growth as previously described.⁶

IN VITRO SUSCEPTIBILITY

Minimum inhibitory concentrations (MIC) were determined using the microdilution method (96-well plate). *Borrelia burgdorferi* cultures in the log phase of growth were counted using a Petroff-Hausser (Hausser Scientific, Horsham, Pa) counting chamber. Duplicate wells containing BSK medium with and without the appropriately diluted antimicrobial agents were inoculated to a final density of 1×10^5 cells/mL of the test organism. After incubation at 34°C for 1 week, the wells were examined by dark-field microscopy for the presence of spirochetes, and the MIC was determined. All wells with negative findings (no spirochetes observed) were transferred (10% vol/vol) to BSK medium without antibiotics, incubated at 34°C for 3 weeks, and examined for spirochetes. The minimum bactericidal concentration (MBC) was the lowest antibiotic concentration from which spirochetes could not be subcultured.

tenderness at the rash site. Two had pustular or vesicular areas in the rash (**Figure**), and 1 had a uniformly erythematous lesion near the site of a previous mastectomy and lymph node dissection. Cephalexin was administered for an average of 8.6 days (range, 2-21 days) prior to presentation, with 5 patients completing the entire course of therapy prescribed (10-21 days) for the rash. Two of 11 patients had a history of penicillin allergy. Eight patients sought care at the Lyme Disease Diagnostic Center because their rash increased in size and/or systemic complaints such as arthralgias or fever developed while they were taking cephalexin. One patient developed a facial nerve palsy, and another developed a facial nerve palsy along with multiple new EM lesions, both within 10 days of completing a prescribed course of cephalexin for 21 and 10 days, respectively. Another patient developed multiple EM lesions after taking cephalexin for 9 days.

All patients were retreated with doxycycline hydrochloride with resolution of their rash and systemic symptoms. One patient had a slight residual facial palsy at 1 month and was then lost to follow-up. The average duration of follow-up for all 11 patients was 13.6 months (range, 1-30 months).

LABORATORY FEATURES

Nine (82%) of 11 patients had laboratory confirmation of *B burgdorferi* infection. Five (45%) of 11 had cultures positive for *B burgdorferi*, 3 from skin specimens alone, 1 from skin and blood specimens, and 1 from blood specimen alone. These 5 patients had taken cephalexin for an average of 9.8 days (range, 5-21 days) before the specimen was obtained that grew *B burgdorferi*. An additional patient whose culture was negative for bacteria had *B burgdorferi* detected by polymerase chain reaction from a skin biopsy specimen. Ten of 11 patients had baseline and follow-up ELISAs for antibodies to *B burgdorferi* performed. Four (40%) of 10 were positive at baseline and 3 seroconverted by their 10- to 20-day follow-up visit. One patient did not have an ELISA performed because of participation in a vaccine efficacy trial. Acute and convalescent immunoblots for *B burgdorferi* antibodies obtained as part of that trial were nondiagnostic.

MIC/MBC TESTING

Table 2 gives the results of MIC and MBC tests comparing cephalexin, cefuroxime axetil, ceftriaxone sodium, and amoxicillin with 7 strains of *B burgdorferi*. Two of the strains tested were the standard laboratory strains B31 (*Ixodes scapularis* tick isolate from New York) and B297 (human spinal fluid isolate). Five additional strains had been isolated from patients evaluated at the Lyme Disease Diagnostic Center, including 1 (B230) from patient No. 7. The MIC for cephalexin ranged from 25 µg/mL

Table 1. Clinical and Laboratory Findings of 11 Patients With Erythema Migrans Who Were Initially Treated With Cephalexin*

Patient No./ Age, y	Rash Duration, d†	Rash Characteristics at LDDC	Dose and Duration (d) of Cephalexin Therapy	Patient Rash Evolution While Receiving Cephalexin	ELISA, Acute/ Convalescent (Index Value)	Culture Results for <i>Borrelia burgdorferi</i>
1/49	18	Tender, warm, with tender adenopathy	250 mg, 4 times daily (13)	Increased in size	0.46 (N)/1.33 (P)	N
2/46	3	Tender, pustular	500 mg, 4 times daily (2)	Increased in size	0.53 (N)/2.58 (P)	N
3/49	25	Uniformly erythematous‡	Unknown dose, 4 times daily (14)	Decreased in size§	0.42 (N)/0.96 (E)	N
4/30	6	Tender	250 mg, 4 times daily (4)	Increased in size with vesiculation	0.31 (N)/0.52 (N)	N
5/40	5	Tender, warm	500 mg, 3 times daily (3)	Increased in size	Not done; nondiagnostic immunoblot	N
6/47	12	Warm	250 mg, 4 times daily (10)	Developed multiple EM lesions with fever	1.2 (P)/1.62 (P)	P
7/20	33	Warm	500 mg, 3 times daily (21)	Decreased in size; new 7th nerve palsy	2.78 (P)/3.12 (P)	P
8/22	20	Ecchymotic	500 mg, 3 times daily (10)	Developed multiple EM lesions with new 7th nerve palsy	1.80 (P)/2.01 (P)	N
9/39	4	Vesicular, warm	250 mg, 4 times daily (4)	Increased in size with paresthesias at rash site	0.21 (N)/0.83 (E)	P
10/47	24	Tender, warm, indurated	500 mg, 4 times daily (10)	Increased in size with fever	1.39 (P)/1.61 (P)	P
11/59	7	Tender, warm	Unknown dose, 4 times daily (4)	Increased in size with fever	0.30 (N)/1.41 (P)	P¶

*ELISA indicates enzyme-linked immunosorbent assay; P, positive; N, negative; E, equivocal; and EM, erythema migrans.

†Prior to presentation at the Lyme Disease Diagnostic Center (LDDC).

‡Rash on shoulder near previous mastectomy and lymph node dissection.

§Rash slightly decreased in size while receiving cephalexin, followed by an increase in size 4 to 5 days after discontinuation of therapy.

||Acute/convalescent immunoblot results: IgM, no bands; IgG, 41; IgM, 41; and IgG, 23, 39, and 41.

¶Serum (not skin) culture findings positive for bacteria.

to 50 µg/mL while the MBC for cephalexin was more than 100 µg/mL in 6 of 7 strains tested.

COMMENT

Erythema migrans is the presenting manifestation in more than 85% of patients with objective evidence of Lyme disease.⁷ Typically, the erythema begins as a macule or papule at the site of the tick bite, which expands in size for days to weeks. Often described as a bull's-eye rash, central clearing is present in fewer than 40% of patients with EM.⁷ Atypical features may include central vesiculation and/or pustule formation, ecchymotic appearance, intense erythema with tenderness and warmth, or induration.⁸ Serologic testing in this early stage is often not helpful.⁷ Recommended therapy for this stage of Lyme disease includes oral doxycycline, amoxicillin, or cefuroxime for 14 days.⁷

Previous reports of in vitro susceptibility testing using a few strains of *B burgdorferi*^{9,10} and a single report of in vivo susceptibility in a mouse model using a *Bor-*



Patient No. 4. Erythema migrans rash with atypical features. Note the uniform erythema with multiple vesicles surrounding the central punctum.

Table 2. Minimum Inhibitory Concentration and Minimum Bactericidal Concentration Testing

Drug	Strain of <i>Borrelia burgdorferi</i>						
	B230	B244	B261	B265	B268	B31	B297
Minimum Inhibitory Concentration (µg/mL) Against <i>B burgdorferi</i>							
Cephalexin	25	50	50	50	25	25	25
Cefuroxime	≤0.1	0.2	0.2	0.2	0.2	0.2	0.2
Ceftriaxone	0.025	0.05	0.05	0.025	0.025	0.025	≤0.012
Amoxicillin	0.2	0.2	0.2	≤0.1	≤0.1	0.2	≤0.1
Minimum Bactericidal Concentration (µg/mL) Against <i>B burgdorferi</i>							
Cephalexin	50	>100	>100	>100	>100	>100	>100
Cefuroxime	0.4	0.8	1.6	1.6	0.4	3.1	1.6
Ceftriaxone	0.1	0.05	0.1	0.05	0.05	0.2	0.4
Amoxicillin	0.8	0.8	0.8	0.2	0.2	3.1	1.6

relia garinii strain, HP1,¹¹ suggested that first-generation cephalosporins would be ineffective for treating Lyme disease in humans. Our study confirms and extends these findings. Based on in vitro study of 7 strains of *B burgdorferi*, including 5 recent clinical isolates, the MIC for the first-generation cephalosporin, cephalexin, was 25 µg/mL to 50 µg/mL, and the MBC was usually greater than 100 µg/mL. The MIC cutoff for susceptibility to cephalexin for other bacteria is less than or equal to 8 µg/mL; an MIC of 16 µg/mL is deemed moderately susceptible. The usual peak serum level of cephalexin after a 500-mg dose is 18 µg/mL.¹² Therefore, cephalexin is inactive against *B burgdorferi* in vitro and would not be predicted to be clinically effective based on achievable blood levels.

These observations are in sharp contrast to certain second- or third-generation cephalosporins and to amoxicillin. For example, the MIC for cefuroxime, a second-generation cephalosporin, was less than or equal to 0.18 µg/mL; the MIC for the third-generation cephalosporin, ceftriaxone, was 0.02 µg/mL; and the MIC for amoxicillin was less than or equal to 0.25 µg/mL.¹⁰ Furthermore, all 3 of these agents are known to be clinically effective for patients with Lyme disease.

Susceptibility testing for *B burgdorferi*, however, is not standardized and has not always correlated with clinical efficacy. For example, macrolide antibiotics such as erythromycin base, azithromycin, and roxithromycin show effective inhibition and killing of *B burgdorferi* in vitro¹³⁻¹⁵ but have not been as successful as β-lactam antibiotics or tetracyclines in animal models^{13,16,17} or in clinical trials in humans.¹⁸⁻²⁰

The findings of this study indicate that the measured in vitro activity of cephalexin and the clinical response to therapy are concordant. All 11 patients who were treated with cephalexin for EM responded poorly to treatment (Table 1). All 11 patients had objective evidence of clinical failure such as an increase in size of the rash (8 patients), development of new EM lesions (2 pa-

tients), and/or occurrence of a new seventh-nerve palsy (2 patients). In addition, *B burgdorferi* could be recovered in culture specimens from 5 patients despite a mean of 9.8 days of treatment with cephalexin (range, 5-21 days). Recovery of *B burgdorferi* during or following therapy with amoxicillin or a tetracycline derivative of greater than 24 hours' duration has never occurred in our experience.^{5,21}

Our findings do not prove that cephalexin is uniformly ineffective for Lyme disease because of the potential for referral bias of those patients failing to improve with treatment. Nevertheless, our observations strongly suggest that cephalexin should not be used for treating patients with Lyme disease and should be used with caution during the summer months for patients with cellulitis in locations where Lyme disease is endemic. The finding that nearly 1 in 35 patients with EM enrolled in Lyme disease studies at our center was initially prescribed cephalexin suggests that the possibility for diagnostic error is substantial. When bacterial cellulitis caused by *S pyogenes* or *S aureus* cannot be distinguished from EM, cefuroxime or amoxicillin-clavulanate potassium would be a preferred choice of therapy, as these drugs are effective for either type of infection.

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Clinical Pearl

C-Reactive Protein Predicts Cardiovascular Disease in Women

In the Women's Health Study, which includes postmenopausal women with no history of cardiovascular disease or cancer, C-reactive protein was the best serum univariate predictor of the occurrence of cardiovascular events over the next three years. The relative risk for events in women with the highest quartile measurement of C-reactive protein compared to the lowest quartile was 4.4 (95% confidence interval, 2.2-8.9). This compared to a relative risk for total cholesterol or low-density lipoprotein cholesterol of 2.4. (*N Engl J Med.* 2000;342:836-843).