REVIEWS OF INFECTIOUS DISEASES • VOL. 11, SUPPLEMENT 6 • SEPTEMBER-OCTOBER 1989
 0162-0886/89/1105-0030$02.00

A Perspective on the Treatment of Lyme Borreliosis

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Lyme borreliosis has become the most common tick-borne infection in the United States. Although both β-lactam and tetracycline antibiotics have been shown to be effective in the treatment of this spirochetosis, the development of optimal therapeutic modalities has been hampered by the lack of reliable microbiologic or immunologic criteria for the diagnosis or cure of this infection. In vitro sensitivity studies have been performed by several laboratories, but there has been no standardization of the methodology for measuring either inhibitory or bactericidal levels. Clinical studies have documented the efficacy of antibiotics, but therapy has failed in as many as 50% of cases of chronic infection. Although new antibiotic regimens appear promising, the optimal treatment of this infectious disease remains to be determined. In this report we review the clinical and experimental rationale for the antibiotic regimens that we currently use and the need for a more standardized approach to treatment trials.

The development of rational therapeutic modalities for Lyme borreliosis has been hampered by the lack of reliable microbiologic or immunologic criteria for its diagnosis or cure. Instead, diagnosis has depended upon a history of potential exposure to tick vectors in an endemic area and the recognition of clinical features associated with acute or chronic Lyme borreliosis. Serologic tests are often negative early in the infection, and the presence of low levels of antibody to *Borrelia burgdorferi* in individuals from endemic areas (where the background seropositivity rate may be as high as 8% [1]) does not necessarily mean that a given syndrome is due to *B. burgdorferi* infection.

In all studies of the treatment of Lyme borreliosis, the clinical response, e.g., resolution of specific signs and symptoms or lack of progression of disease, has been the primary indicator of efficacy. Because a uniform case definition is lacking, studies often differ in their criteria for a successful outcome. In several studies, therapy for erythema migrans (EM) was followed by the persistence of symptoms such as arthralgias, headache, and lethargy in up to 50% of patients [2]. It is not clear whether these symptoms were due to the persistence of a small number of pathogens or were ascribable to a postinfectious syndrome. Persistent *B. burgdorferi* infection can produce various insidious and chronic dermatologic, neurologic, and rheumatologic manifestations [3–15]. The pathophysiologic mechanisms involved in the chronic phase of this illness remain incompletely defined. It has not been determined whether persistent symptoms are secondary to some immunologic process or whether anything short of total eradication of *B. burgdorferi* is sufficient for ultimate cure and resolution of symptoms.

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Clinical Manifestations

Lyme borreliosis has a wide array of clinical manifestations. Some authors have divided this illness into three distinct stages [16–18]: EM or a flu-like illness, neurologic or cardiac involvement, and arthritis. Although this scheme is straightforward, it is misleading in that the timing and range of organ system involvement vary markedly among individual patients.

Following a tick bite with inoculation of *B. burgdorferi* into the skin, one-half to three-quarters of infected patients develop a characteristic EM skin lesion [18]. The microbial load increases rapidly during this early phase of infection, as evidenced by the isolation of the organism from cultures of skin lesions [19] and occasionally from those of blood and CSF and by the demonstration of *B. burgdorferi* histologically in affected tissues. The early hematogenous spread of this organism is also evidenced by the frequency of multifocal EM. This rapid bacterial dissemination is associated with a wide array of acute systemic manifestations, including meningitis [17, 20], myocarditis [21, 22] with or without heart block,

hepatitis [23], myositis [24], and arthritis [15, 25, 26]. More commonly, milder and less specific manifestations such as fever, conjunctivitis, meningismus, headache, arthralgias, and myalgias develop at this phase of the infection [18]. In the chronic phase of the illness, *B. burgdorferi* is more difficult to isolate or identify in affected tissues and the bacterial load appears to be lower than during the acute phase. Localized inflammatory processes may occur in one or more organ systems (i.e., the nervous system, the musculoskeletal system, and the skin).

In Vitro Sensitivity Testing and Studies in Animals

Studies on the in vitro sensitivity of *B. burgdorferi* to antibiotics are few and have involved only a small number of isolates (table 1). Since there is neither an established methodology to determine the MICs and MBCs of antibiotics for slowly dividing organisms nor a clear understanding of the relation between in vitro sensitivity and in vivo efficacy in this type of infection, placement of these studies in an appropriate context is difficult. Furthermore, it is hard to compare the studies directly because dissimilar methods were used, e.g., different inocula of *B. burgdorferi*, organisms at various phases of growth (early log phase, late log phase, or stationary phase), and exposure of the spirochete to antibiotics for different periods. Standardized methodology is clearly needed. However, even with these limitations, in vitro studies can provide insights useful in the development of in vivo efficacy studies.

Data from in vitro studies of the sensitivity of *B. burgdorferi* to various antibiotics are summarized in table 1. Although both the time of incubation of the organism with the antibiotics and the criteria for inhibition or killing varied among the studies, several trends are apparent. The tetracyclines, including tetracycline hydrochloride, doxycycline, and minocycline, are all effective and are similar in their activity against *B. burgdorferi* [28, 30–32]. Among the β-lactam antibiotics, penicillin, ampicillin, amoxicillin, ceftriaxone, and cefotaxime [27, 28, 30–32] are all active against *B. burgdorferi*. However, the β-lactams differ in their relative potency. In studies in which the same bacterial isolates were used, *B. burgdorferi* was approximately two to three times more susceptible to ampicillin than to penicillin. Ceftriaxone was as much as 100 times more active than penicillin in terms of its ability to kill *B. burgdorferi* in vitro [29, 31, 32]. Although this organism was highly sensitive to erythromycin in vitro, erythromycin was less efficacious than penicillin or tetracycline in vivo [2].

In investigations of the kinetics of killing of *B. burgdorferi* by penicillin, ceftriaxone, erythromycin, or tetracycline, it was determined that 72–96 hours are necessary for the killing of 99% of the or-

Table 1. MICs and MBCs for *B. burgdorferi* of antibiotics commonly used for treatment of Lyme borreliosis.

Reference, antibiotic	Concentration (mg/L)*		Duration of assay†	No. of strains tested
	Mean	Range		
27				
Penicillin G	1.10	0.5–3.0	4	7
Ampicillin	0.47	0.25–1.0		
Tetracycline	0.71	0.25–2.0		
Erythromycin	0.15	0.06–0.25		
28				
Penicillin G	0.93	0.25–2.0	5	5
Ampicillin	≤0.25	0		
Tetracycline	≤0.79	≤0.25–2.0		
Erythromycin	≤0.06	0		
Doxycycline	≤0.63	≤0.25–2.0		
Minocycline	≤0.13	≤0.12–0.25		
29				
Penicillin G	(6.5)		42	1
Ceftriaxone	(0.04)			
Erythromycin	(0.05)			
30				
Penicillin G		0.005–0.08	3	
		(0.08–2.5)		
Minocycline		0.09–0.17		
		(1.35–5.43)		
Erythromycin		0.03–0.01		
		(0.2–1.6)		
31				
Penicillin G		(0.50–8.0)	8	10
Amoxicillin		(0.25–1.0)		
Ceftriaxone		(0.06–0.25)		
Tetracycline		(0.12–1.0)		
Erythromycin		(<0.06–0.12)		
32				
Penicillin	0.50	0.1–1.0	2	5
	(7.96)	(2.0–>50)		
Ceftriaxone	0.03	0.01–1.0		
	(3.81)	(1.0–>50)		
Tetracycline	0.14	0.01–1.0		
	(4.10)	(2.0–6.0)		
Erythromycin	0.04	0.01–1.0		
	(2.17)	(0.1–10)		

* Concentrations shown in parentheses are MBCs; all other values are MICs. Data are compiled from various studies.

† Number of hours the organisms were incubated with antibiotic before assay.

ganisms [32]. Increasing the concentration of the β-lactam antibiotics did not markedly alter the rate of killing. The kinetics of the in vitro killing of *B. burgdorferi* are remarkably similar to those for *Treponema pallidum* [33, 34] in that prolonged exposure to antibiotics is necessary for effective killing.

The therapeutic principles used in the treatment of syphilis may also be relevant in the treatment of Lyme borreliosis [35]. For instance, for eradication of *T. pallidum* in an animal model, effective levels of penicillin must be maintained to ensure killing because slowly multiplying organisms may regenerate during the time that the antimicrobial concentrations drop to subinhibitory levels [35]. For this reason, an agent such as ceftriaxone, with its unique pharmacologic (long half-life) properties, may prove most effective in the treatment of *B. burgdorferi* infection. Two studies of *B. burgdorferi* infection—one in hamsters [29] and the other in gerbils [31]—demonstrated ceftriaxone and tetracycline to be more active than penicillin in eradicating acute *B. burgdorferi* infection from various organs. However, because the dosing schedule of each antibiotic was identical in both studies, the pharmacokinetic differences among ceftriaxone, tetracycline, and penicillin must be recognized in the interpretation of these results. Although in vitro data should be considered when therapeutic regimens are designed for *B. burgdorferi* infection, the relation of the MIC or MBC of a given drug for slowly dividing organisms such as *B. burgdorferi* and in vivo effectiveness has not been established. Therefore, the utility of MIC and MBC data in the design of therapeutic regimens remains limited, and until better-defined animal models are established, these data should be used only as a general guide.

Studies in Humans

Erythema migrans. The effectiveness of antimicrobial agents in the treatment of EM was demonstrated as early as 1946 [36]. Various treatment regimens have included several forms of tetracycline and β-lactam antibiotics. The response to therapy has generally been good, especially if the illness associated with EM is mild [2, 19]. In a randomized, controlled study performed by Steere et al. [2], tetracycline was thought to be superior to penicillin or erythromycin (with all drugs given at a dosage of 250 mg four times daily for 10 days) in preventing "major" late complications of Lyme disease, including meningoencephalitis, myocarditis, or recurrent attacks of arthritis, although the differences between tetracycline and penicillin were not statistically significant. However, "minor" late complications, such as facial palsies, supraventricular tachycardia, brief episodes of arthritis, fatigue, and lethargy, occurred in 38%–50% of patients irrespective of the treatment regimen.

In addition, well-documented treatment failures have been reported. These results have led other investigators to alter treatment regimens using β-lactam antibiotics and tetracycline. Weber et al. [37] reported that 27% of patients with EM develop later neurologic or musculoskeletal manifestations of the infection regardless of whether penicillin, tetracycline, or amoxicillin plus clavulanate was used. Berger [38] reported on the antibiotic treatment of 117 patients with EM. Although this was a nonrandomized study, several interesting observations were reported. The treatment of mild EM was effective in all patients. In patients with EM accompanied by fever, marked musculoskeletal pain, headache, and fatigue, the response to therapy was not as uniform. In all, six of 16 patients who had more severe illness accompanied by EM and who were treated with 250–500 mg of penicillin required retreatment because of persistent illness. However, when probenecid was added to the regimen, only one of 22 required retreatment. These results, although preliminary and retrospective, are quite intriguing, suggesting that, as in syphilis, sustained bactericidal levels of antibiotics may be required for effective killing of the organism.

Recently, in a small study by Dotevall et al. [39], nine patients with mild peripheral neurologic disease were successfully treated with doxycycline.

Chronic Lyme disease. β-Lactam antibiotics have been the standard therapy for chronic Lyme borreliosis. High-dose intravenous penicillin has not been universally successful. In studies by Steere et al. [40] of 43 patients with arthritis treated with either 3 weeks of benzathine penicillin or 10 days of penicillin G, 35% and 55%, respectively, had complete resolution of their arthritis. In contrast to arthritis, acute meningitis or meningoencephalitis due to *B. burgdorferi* seems quite responsive to high-dose penicillin therapy. This efficacy may reflect the breakdown of the blood-brain barrier, which allows high, more sustained levels of penicillin within the CNS. In several reported cases acute CNS infection has progressed during penicillin therapy, but these cases are rare [41–43].

Meningopolyradiculitis (Bannwarth's syndrome) does not uniformly respond to treatment with penicillin, but the progression of symptoms and signs is halted by penicillin therapy in most cases [41, 44, 45]. However, of patients with severe neurologic signs, such as spastic paraparesis, more than 50% will continue to suffer from disability due to this disease for months to years after treatment [44, 45]. It is not clear whether this long-term effect is due to a persistent, smoldering infection; to immune autoreactivity triggered by the infection; or to pathologic changes that occur prior to treatment. Similarly, antibiotic treatment of acrodermatitis atrophicans produces resolution of skin involvement in only ~50% of patients. In addition, ~50% of these patients continue to have extracutaneous manifestations of Lyme disease after therapy [8]. Thus, failure rates of ≥50% are being reported in some series for the treatment of chronic rheumatologic, dermatologic, or neurologic disease due to *B. burgdorferi*. Clearly, alternative therapies are needed.

We recently evaluated ceftriaxone as an alternative in the treatment of late Lyme borreliosis [32] in patients with neurologic or rheumatologic disease. In our initial study [43], seven patients with active, late Lyme disease (i.e., CNS dysfunction, peripheral neuropathy, and/or arthritis) refractory to high-dose penicillin were treated with 4 g of ceftriaxone/d in divided doses. After treatment with ceftriaxone, all objective and subjective evidence of arthritis resolved. Five of the six patients with limb paresthesias reported improvement, which was documented by an increase between pre- and post-therapy studies in the mean sensory amplitude and nerve conduction velocity on electromyography. All seven patients reported improvement on resolution of chronic fatigue. Similarly, Pal et al. [41] reported a patient with Lyme encephalitis recalcitrant to penicillin therapy who responded promptly to cefotaxime therapy. From these studies, it appears that ceftriaxone or related third-generation cephalosporins may be more active than penicillin in the treatment of late Lyme borreliosis.

We next performed a randomized comparison of ceftriaxone and penicillin for the treatment of late Lyme borreliosis. Admission criteria were a history of physician-observed EM and/or evidence of specific immunologic reactivity to *B. burgdorferi* and objective evidence of involvement of two or more of the following organ systems: central and peripheral nervous system, cardiovascular system, and musculoskeletal system. Twenty-three patients were randomized to receive penicillin (4 million units every 4 hours for 10 days) or ceftriaxone (2 g twice daily for 14 days) [46]. Prior to therapy, relapsing oligoarticular arthritis was documented in seven of the 10 patients in the penicillin group and in nine of the 13 patients in the ceftriaxone group. Seven patients receiving penicillin and nine receiving ceftriaxone also had symptoms of mild encephalopathy.

After therapy, five of the 10 patients given penicillin (50%) continued to have recurrent oligoarticular arthritis, fatigue, and memory difficulties. Three of four penicillin-treated patients with peripheral neuropathy had resolution, as evidenced by both the disappearance of symptoms and abnormalities on neurophysiologic testing. One patient with complete heart block was treated with penicillin; his conduction abnormality resolved, but he developed arthritis 2 months after completion of therapy. In contrast, none of the 13 patients randomized to ceftriaxone had objective evidence of persistent disease activity, although one described ongoing fatigue and memory difficulty and three continued to complain of mild arthralgias.

The ceftriaxone arm of the study was extended to an additional 31 patients, who were treated daily with either 2 g (14 patients) or 4 g (17 patients). Of these 31 patients, three had persistent neuropathy, two had persistent encephalopathy, and three had no improvement in arthritis. Overall, 13% of this group of patients failed to respond to therapy. The rates of response to the two doses of ceftriaxone were similar (~85%).

Discussion

For approximately 40 years, penicillins have been used empirically for the treatment of disease now known to be due to *B. burgdorferi* [36, 47–49]. Steere et al. [2, 50] performed several prospective studies and unequivocally established the efficacy of penicillin and tetracycline in the treatment of early infection with *B. burgdorferi*. However, in each treatment study, whether it was concerned with early or late disease, a significant number of treatment failures occurred. For example, in the randomized prospective study evaluating the use of penicillin and tetracycline for the treatment of EM, ~50% of the patients given either regimen subsequently developed "minor" manifestations of disease and several treated with penicillin went on to develop "major"

manifestations [2, 51]. For chronic rheumatologic, dermatologic, and neurologic disease, therapy with penicillin has been associated with a failure rate of ⩾50% [40, 45]. Thus, it appears that although tetracycline and penicillin are clearly efficacious, they are not uniformly effective. Studies for optimization of these therapies are certainly warranted.

In vitro antimicrobial susceptibility studies have been reported by several laboratories [27–32]. However, because these investigations were not performed in a standardized manner, comparison of results is difficult. Standardization of the period of co-incubation of the organism with a given antibiotic is an important variable in determining the ability of the antibiotic to kill or inhibit the growth of *B. burgdorferi* [32]. Variability of this parameter between studies could therefore account for differences in the reported susceptibility of the organism.

The finding that prolonged exposure (i.e., for as long as 72–96 hours) is necessary for effective killing of *B. burgdorferi* may have important therapeutic implications [32]. Similar kinetics of killing have been noted for *T. pallidum* [34, 35]; it has been shown in an animal model that *T. pallidum* will regrow if penicillin levels are allowed to fall into a subinhibitory range [35]. A similar phenomenon may occur in *B. burgdorferi* infection. In animal models, ceftriaxone, with its prolonged half-life and higher level of activity, is more effective than penicillin. However, given the differences in the pharmacokinetics of these drugs, their efficacy cannot be measured on a milligram-per-kilogram basis. Therefore, it remains to be determined whether in vitro sensitivity studies performed in a standardized manner correlate with in vivo efficiency and whether the greater efficacy of ceftriaxone is due to the ability of this agent to remain above the inhibitory level for the entire period of therapy.

Any recommendations with regard to the effective treatment of Lyme borreliosis must take into account the full extent of the infection. In early disease, therapy should be geared toward the achievement of adequate tissue levels, especially in the CNS, because of the possibility of early dissemination. Perhaps more attention should be given to choosing the form of tetracycline that best penetrates the CNS, as suggested by Dotevall et al. [39]. Although lower doses of tetracycline or penicillin (250 mg four times daily) may be effective when infection is localized to the skin, these regimens may not provide adequate tissue levels and thus may be relatively ineffective once the infection disseminates [2, 19]. This point is especially apparent when one considers that the peak levels of these drugs in tissues like the nervous system are at or below the concentration needed to inhibit or kill the organism in vitro. Recently, the *Medical Letter* recommended guidelines for the treatment of Lyme disease [52]. In general, we have found these guidelines to be useful. However, our therapeutic approach is geared toward attaining higher and persistently elevated serum and tissue levels (table 2). We think that in early disease, especially when associated with symptoms of systemic involvement, a more aggressive approach than 250 mg of tetracycline four times daily is necessary. The erratic absorption of tetracycline by the gastrointestinal tract and the relatively low serum and CNS levels achieved by this dose (2.0 and 0.2 μg/mL, respectively), even under optimal conditions, mean that serum levels are inadequate as judged by the MICs reported for several strains of *B. burgdorferi* by various investigators [27–29]. Treatment failures with tetracycline have been reported [51].

It is apparent that *B. burgdorferi* disseminates hematogenously in a sizable group of patients (with as many as 50% having multiple EM lesions) and that high tissue levels of antimicrobial agents may be needed to eradicate the infection. It would therefore appear prudent to treat patients with tetracyclines that are better absorbed and that produce higher levels in critical tissues. Doxycycline (100 mg two or three times daily) or minocycline (100 mg twice daily), which reach higher levels in serum and tissue (including the nervous system [39]) and have a lower propensity to cause gastrointestinal distress, are good alternatives to other tetracyclines. Amoxicillin (500 mg three times daily) plus probenecid, with its excellent absorption by the gastrointestinal tract and its activity in vitro, would seem a better choice than penicillin. If tetracycline is to be used, we suggest that higher doses (500 mg four times daily) be given to adult patients. Treatment should be continued for ~3 weeks. If any symptoms or signs are suggestive of CNS involvement, appropriate diagnostic tests should be performed, including examination of the CSF. Regardless of the chronicity of infection, if CNS involvement is discovered or there is significant compromise of an organ system as a result of infection, the patient should receive parenteral therapy so that adequate CNS drug levels are attained. Treat-

Table 2. Treatment of Lyme disease.

Type of disease, drug	Adult dosage	Pediatric dosage
Early		
Amoxicillin	500–1,000 mg tid × 21 d	40 mg/(kg·d), divided, × 21 d
plus probenecid (optional)	500 mg tid × 21 d	
Doxycycline	100 mg bid or tid × 21 d	
Erythromycin*	250 mg qid × 10–21 d	30 mg/(kg·d), divided, × 10–21 d
Neurologic		
Mild (Bell's palsy)		
Doxycycline	100 mg bid or tid × 21–30 d	
Amoxicillin	500–1,000 mg tid	
plus probenecid	500 mg tid × 21–30 d	
More serious CNS disease		
Penicillin G	24 million units/d, divided, × 14–21 d	250,000 units/(kg·d) iv, divided (q4h), × 14–21 d
Ceftriaxone	2 g/d × 14 d	75–100 mg/(kg·d) iv
Cardiac		
Mild		
Doxycycline	100 mg bid or tid × 21 d	
Amoxicillin	500–1,000 mg tid × 21 d	40 mg/(kg·d), divided, × 21 d
plus probenecid	500 mg tid × 21 d	
More serious		
Penicillin G	24 million units/d, divided, × 14–21 d	250,000 units/(kg·d) iv, divided (q4h), × 14–21 d
Ceftriaxone	2 g/d × 14 d	75–100 mg/(kg·d) iv
Arthritis		
Ceftriaxone	2 g iv × 14–21 d	75–100 mg/(kg·d) iv
Doxycycline†	100 mg bid × 30 d	
Amoxicillin	500–1,000 mg tid × 21 d	
plus probenecid	500 mg tid × 30 d	

* Alternative therapy.
† Under investigation.

ment of this infection, especially in its early stages, is associated with a Jarisch-Herxheimer reaction in 10%–20% of patients [38].

The aim of treatment of early Lyme disease during pregnancy is not only to treat the infection and prevent long-term sequelae but to eliminate the infection as quickly as possible so as to prevent congenital transmission to the fetus [53–55]. Recently, Weber et al. [56] reported the congenital transmission of *B. burgdorferi* to an infant whose mother had been treated with 1 million units of oral penicillin for 7 days. Given the significant failure rate described by Steere et al. [2] in patients treated with 250 mg of oral penicillin (more than 50% of whom developed "minor" and "major" disease), it would seem reasonable to administer more vigorous treatment to pregnant patients with acute EM. No study has established the optimal treatment in this instance; however, either oral amoxicillin plus probenecid or parenteral ceftriaxone has been used. Further studies must establish the duration of therapy necessary to eradicate this infection and thus to prevent congenital transmission.

In our studies [43, 46], we found ceftriaxone to be significantly more effective than penicillin in the treatment of late Lyme borreliosis. Long-term investigations are needed to determine whether the patients treated with ceftriaxone remain in remission. Although ceftriaxone appears to be promising, it is still associated with a 15% failure rate [52]. A topic for further research is whether a more prolonged course of therapy would be useful in decreasing this rate of relapse. In addition, the efficacy of various antimicrobial agents for the treatment of the different manifestations of early and chronic Lyme borreliosis must be assessed. However, until technology is available for ready culture of *B. burgdorferi* or identification of persistent infection, the adequacy of therapy will remain speculative, as will the correlation of various syndromes with persistent infection.

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