Diagnostic Microbiology and Infectious Disease xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Diagnostic Microbiology and Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio

Is the risk of early neurologic Lyme borreliosis reduced by preferentially treating patients with erythema migrans with doxycycline?☆

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ARTICLE INFO

Article history:
Received 27 November 2017
Received in revised form 23 January 2018
Accepted 28 January 2018
Available online xxxx

Keywords:
Lyme borreliosis
Erythema migrans
Borrelia burgdorferi sensu lato
Neurologic Lyme borreliosis
Doxycycline
Amoxicillin
Cefuroxime axetil
Azithromycin

ABSTRACT

Doxycycline is highly effective treatment for early neurologic Lyme borreliosis (NLB). Nineteen studies were reviewed to determine if treatment of patients with erythema migrans with other oral antibiotics would increase the risk for developing NLB. In the eight studies that directly compared doxycycline to another antibiotic, the pooled difference indicated a 0.2% greater risk of developing NLB in doxycycline-treated patients (95% CI: −1.0%, +1.4%; $P = 0.77$), with an estimated heterogeneity of 0.0%, $P = 0.58$. Overall, in the 19 studies, NLB was reported in 8/828 (1.0%; 95% CI: 0.42%, 1.89%) doxycycline-treated patients versus 6/1022 (0.6%; 95% CI: 0.22%, 1.27%) patients treated with other antibiotics ($P = 0.42$). Based on the 95% CI calculation (−0.5%, +1.40%), patients receiving nondoxycycline treatment regimens collectively might have at most a 0.5% greater risk for developing NLB. Available data suggest that oral doxycycline is not superior to comparators for preventing NLB in patients receiving treatment for erythema migrans.

1. Introduction

Lyme borreliosis is the most common tick-transmitted infection in North America and Europe. The infection is caused by *Borrelia burgdorferi* sensu lato. The most common clinical manifestation is the skin lesion referred to as erythema migrans. In untreated United States patients with erythema migrans, the skin lesion will eventually resolve, but the majority of such patients will go on to develop an extracutaneous manifestation, most frequently arthritis. Among 55 untreated United States patients with erythema migrans, at least 61.8% developed an objective extracutaneous manifestation, such as Lyme arthritis. A neurologic manifestation, such as seventh cranial nerve palsy, lymphocytic meningitis, and/or radiculopathy, developed in 10.9% of the 55 patients (Steere et al., 1987). At the time of initiation of antibiotic treatment of United States patients with erythema migrans, at least 20% of those with a single skin lesion and at least 40% of those with multiple skin lesions have been found to be spirochetemic (Wormser et al., 2001; Wormser et al., 2005). These and other data (Luft et al., 1992) raise the question of whether *B. burgdorferi* may have already spread to other organs outside of the skin, including the nervous system, in certain patients whose only objective clinical manifestation is erythema migrans. In Europe, natural history studies of untreated patients with erythema migrans have not been reported, but about one-half of patients with meningoradiculitis, a typical early neurologic manifestation known as Bannwarth's syndrome, were found to have a concomitant or a recent erythema migrans skin lesion (Ackermann et al., 1984; Kohler and Thoden, 1987; Ogrinc et al., 2016). The skin lesion appears several days to a few months before the onset of neurologic signs and symptoms, raising the question of spread of Lyme borrelia to the nervous system before the onset of clinical signs of neurologic involvement. Furthermore, in European children with multiple erythema migrans skin lesions, a mild pleocytosis in cerebrospinal fluid (CSF) was found in 18%–26% of these patients (Arnez et al., 2002a), whereas 5/152 (3%) adults with multiple erythema migrans skin lesions had a CSF pleocytosis (Stupica et al., 2018). None of these patients had clinical signs/symptoms of (central) nervous system involvement.

Among the oral antibiotics used to treat patients with erythema migrans, only doxycycline has been demonstrated in clinical trials to be as effective as parenteral antibiotic therapy with ceftriaxone for

☆ Short summary: Available data indicate that doxycycline is not superior to comparators for preventing the development of early neurologic Lyme borreliosis in patients receiving treatment for erythema migrans.

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https://doi.org/10.1016/j.diagmicrobio.2018.01.025
0732-8893/

Table 1
Neurologic Lyme borreliosis in patients with erythema migrans treated with doxycycline, cefuroxime axetil, amoxicillin, or azithromycin in the United States (US) and Europe (Eu).

Antibiotic	Number of studies[a]		Median duration (days) of EM before treatment	Neurologic complications		Manifestation (onset after the beginning of antibiotic therapy, days)	
				No. (%; 95% CI)			
	Europe	US		Europe	US	Europe	US
Doxycycline	6	6		4/522 (0.8, 0.21–1.95)	4/306 (1.3, 0.36–3.31)	PFP (20); PFP+meningitis (50); MR (~90); MR (~120)	PFP (23); PFP (2); PFP (12); Meningitis (18)
	12		**7**[b]	**8/828 (1.0, 0.42–1.89)**		**PFP (5p), Meningitis (1p), MR (2p)**	
Cefuroxime axetil	2	3		0/185 (0, 0.00–1.97)	1/141 (0.7, 0.02–3.89)	-	Severe headache, vertigo, dizziness (within the first 9 months)[c]
	5		4	1/326 (0.3, 0.01–1.70)		Headache, vertigo, dizziness (1p)	
Amoxicillin	2	2		2/138 (1.4, 0.18–5.14)	0/119 (0, 0.00–3.05)	Meningitis (14); PFP (NA)	-
	4		3	2/257 (0.8, 0.09–2.78)		Meningitis (1p), PFP (1p)	
Azithromycin	7	2		1/312 (0.3, 0.01–1.77)	2/127 (1.6, 0.19–5.57)	MR (~35)	Radicular pain, memory loss, normal CSF cell counts (~120); Meningitis (>14–20)[d]
	9		4	3/439 (0.7, 0.14–1.98)		Meningitis (1p), MR (1p), Radiculitis (1p)	
All antibiotics except doxycycline	10	5		3/635 (0.5, 0.10–1.37)	3/387 (0.8, 0.16–2.25)		
	15		**4**[e]	**6/1022 (0.6, 0.22–1.27)**		**Meningitis (2p), PFP (1p), Radiculitis (1p), MR (1p), Headache, vertigo, dizziness (1p)**	

EM = erythema migrans; PFP = peripheral facial palsy; MR = meningoradiculitis; p = patient; NA = not available.

[a] The majority of studies included more than one antibiotic shown on the table.

[b] Data available for 791/828 patients.

[c] Time after the beginning of antibiotic treatment not exactly stated.

[d] Days after the beginning of antibiotic treatment not exactly stated; however, the patient might have had meningitis at enrollment.

[e] Data available for 776/1022 patients.

treatment of patients with early neurologic manifestations of Lyme borreliosis (Ljøstad et al., 2008). Other oral antimicrobials have not been systematically studied. Thus, a reasonable question to raise is whether treatment of patients with erythema migrans with oral antibiotics other than doxycycline is associated with an increased risk for development of early neurologic Lyme borreliosis.

2. Methods

Clinical trials in which patients with erythema migrans were treated with currently recommended oral antibiotic regimens (Wormser et al., 2006) were reviewed. Data were collected by searching PubMed in July 2017 using the queries "erythema migrans AND treatment," "erythema migrans AND antibiotic," and "erythema migrans AND doxycycline OR amoxicillin OR cefuroxime OR azithromycin OR penicillin" with no limits for year of publication. To be evaluable, clinical follow-up of patients had to be at least 6 months. The focus of the review was on doxycycline, amoxicillin, cefuroxime axetil, and azithromycin, i.e., on antibiotics widely used for treatment of erythema migrans in the United States as well as in Europe. Subjects treated with antibiotic regimens that consisted of amoxicillin plus probenecid or amoxicillin plus clavulanic acid were excluded, as were those who received one dose of ceftriaxone followed by doxycycline.

Count data were summarized with frequencies and percentages. Ninety-five percent confidence intervals (CIs) for proportions were computed using exact methods. Two-tailed Fisher's exact test was used for all bivariate comparisons of proportions. P values < 0.05 were considered statistically significant.

For the eight studies that provided a direct comparison of doxycycline with another antibiotic, we estimated the difference in proportions in neurologic outcomes using a meta-analytic approach. The pooled risk difference was computed using the DerSimonian and Laird approach. Effect heterogeneity was expressed using I^2 and tested using Cohen's Q. Because the studies evaluated used a variety of doses and antibiotics in the comparisons, we estimated a distribution of effects rather than a single fixed effect. As such, random-effects models were generated regardless of degree of heterogeneity (Borenstein et al., 2009). Egger's test was used to estimate the degree of publication bias. To compare the duration of erythema migrans prior to treatment between study groups, a random-effects weighted difference in means was computed. Estimates are given with 95% CIs. Analyses were conducted in Stata (version 14.2, StataCorp, College Station, TX) using the METAN suite of commands.

3. Results

Nineteen studies (Dattwyler et al., 1990; Massarotti et al., 1992; Nadelman et al., 1992; Strle et al., 1992; Strle et al., 1993; Weber et al., 1993; Luger et al., 1995; Luft et al., 1996; Strle et al., 1996; Dattwyler et al., 1997; Arnez et al., 1999; Barsic et al., 2000; Arnez et al., 2002b; . Eppes and Childs, 2002; Wormser et al., 2003; Cerar et al., 2010; Nizic et al., 2012; Stupica et al., 2012; Arnez and Ruzic-Sabljic, 2015) were considered evaluable, comprising 1850 predominantly adult patients with erythema migrans; 1157 of these patients were from Europe and 693 were from the United States (Tables 1 and 2). Information on whether multiple erythema migrans skin lesions were present was available for all but one United States study (Massarotti et al., 1992); the missing data from this study were for 38 patients. Multiple erythema migrans occurred more often in patients treated with doxycycline compared with patients who received other antimicrobials (142/806 [17.6%] versus 86/1006 [8.5%], $P < 0.0001$). Additionally, multiple erythema migrans skin lesions occurred more often among United States patients compared with European patients (202/655 [30.8%] versus 26/1157 [2.2%], $P < 0.0001$). Data on duration of erythema migrans before treatment were significantly more often available for