



CASE REPORT / ПРИКАЗ БОЛЕСНИКА

The influence of early antibiotic therapy on the clinical manifestations in patients with early Lyme disease

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SUMMARY

Introduction/Objective Lyme borreliosis is a multisystem infectious disease caused by *Borrelia burgdorferi* spirochetes transmitted by the bite of an infected tick. The disease manifestations are very different, with the skin, joints, heart, and nervous systems being most often affected.

The aim of this study was to find out whether there are significant differences in the appearance of symptoms and signs of the disease between the subjects who did / did not receive prophylactic, early antibiotic therapy, after the tick bite in patients diagnosed with the early phase of Lyme borreliosis.

Methods The study was carried out on 2,070 patients, who were treated or examined at the Clinic for Infectious and Tropical Diseases in the 1989–2004 period. The patients were divided into group A (n = 591), in which they were given early antibiotic therapy, and group B (n = 1,479), in which they were not. The antibiotic therapy was used within five days of a tick bite in patients with a probable infection, who, at the time, did not have any symptoms or signs. The applied antibiotics included cephalosporins, macrolides, tetracyclines, semisynthetic penicillins, repeatedly for seven or 14 days, or benzathine benzylpenicillin once only.

Results The disease developed in a statistically significantly larger number of patients who were not given early antibiotic therapy (537/1,479) than in those who received the therapy (10/951), i.e. the ratio was 36.3% vs. 1.7%. We concluded that only two antibiotics were sufficient for optimal prevention: doxycycline and ampicillin, administered for seven days. The applied antibiotics showed a high statistically significant efficacy, ranging from 93.7% (cephalosporins) to 99.4% (macrolides).

Conclusion The application of early antibiotic therapy after a tick bite was effective in preventing the early phase of Lyme borreliosis, while in the case of infection it prevented the development of extracutaneous manifestations.

Keywords: Lyme disease; tick; antibiotics; prophylaxis

INTRODUCTION

Lyme borreliosis (Lb) is a multisystem infectious zoonotic disease caused by the *Borrelia burgdorferi* (Bb) spirochetes transmitted by a bite of an infected tick of the genus *Ixodes*. The disease manifestations are very different, with the skin, joints, heart, and nervous systems being most often affected.

The tick bite is the primary mode of infection, and the infection can occur via the conjunctiva or micro trauma that occurs after the tick destruction and skin irritation by its contents [1].

Ixodes ricinus has been proved to be a vector in our country. The infection occurs after one to three days, and rarely within 24 hours, due to inappropriate tick removal [2, 3]. The risk of developing Lyme disease after the bite of an infected tick is 1–4%, while asymptomatic infections range up to 26% in the endemic area [4, 5]. There is a greater risk of the occurrence of manifest illness in children, as well as of the late stage development in people with an asymptomatic infection.

Depending on the stage and extent of the disease, the duration of antibiotic therapy for skin manifestations at the early stage is four to six weeks, while for extracutaneous manifestations the duration is about two months. At the late stage, antibiotic treatment lasts up to 16 weeks, i.e. until the loss of subjective symptoms and clinical signs of the disease [1, 6, 7, 8].

The fact that it affects multiple organs and systems, the development of the late stage of the disease with definite tissue and organ damage, the onset of autoimmune diseases, recurrence and disability, and a possible death outcome were the subject of research in many clinical studies in terms of disease prevention and recommendations for the use of antibiotic therapy after the tick bite, and before the manifestation of the disease [9, 10].

Most authors consider that neither the routine use of antibiotics nor serological testing is necessary just after the tick bite [11, 12]. However, the aforementioned therapy is justified in endemic areas in cases of repeated bites and of serious suspicion concerning the possibility of an infection [9, 13].

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One study involving 600 patients showed that the use of antibiotic therapy was unnecessary due to a small number of infected persons (1.4%) in patients who did not receive an antibiotic after the tick bite, but the same authors recommended carrying out additional studies concerning this subject [14].

Due to the early dissemination of the cause of the disease, the difficulty in diagnosis, and major problems in the treatment of infected patients, particularly in the late stage of the disease, there are opinions that, if there is a suspicion of an infection after the bite, it is justified to apply antibiotics for up to two weeks [6, 8].

The aim of this paper is to determine the effect of prophylactic, i.e. early application of antibiotic therapy on the clinical manifestations in the early phase of Lb. For the purpose of this study, prophylactic antibiotic therapy was defined as the use of antibiotics up to five days after the tick bite in individuals with suspected Bb infection who did not show clinical symptoms and signs of the disease at the time of the application of antibiotics.

METHODS

The study was designed as a retrospective-prospective cohort study. It initially included 2,470 patients who were treated at the Clinic for Infectious and Tropical Diseases of the Military Medical Academy (MMA), Belgrade, Serbia, or examined at the outpatient clinic in the period between January 1, 1989 and December 31, 2004; out of 400 excluded patients 207 did not show up for follow-up monitoring, and 193 received early antibiotic therapy. The study did not include patients who had a positive serological reaction to the Bb antigens at the first examination, i.e. those who had previously developed an infection.

All the patients were classified into two categories. The first category consisted of people who came to the Clinic because of a tick bite. The presence of probable Bb infection was based on the existence of at least one of the following criteria: the presence of Bb in the removed tick; the tick's presence in the skin for more than 48 hours; data on inappropriate tick removal; and the presence of the antibodies to Bb antigens in the serum after four to six weeks. In some patients, based on the clinician's assessment, early antibiotic therapy was applied, while in others it was not.

The second category included patients who came with some of the symptoms and were diagnosed with the early phase of Lyme disease. The diagnosis was based on a characteristic change in the skin, i.e. erythema migrans (EM), clinical picture and the course of the disease, an increase in antibody titer against Bb antigens in two consecutive serum samples within two to four weeks (IIF) or on the positive result after four to six weeks (ELISA), response to antibiotic therapy, exclusion of other related diseases, data concerning the tick bite, and stay in the endemic area.

A total of 2,070 patients were divided into group A, in which early antibiotic therapy was applied, and group B, in which it was not.

The disease symptoms included headaches, myalgia, arthralgia, loss of concentration, sleep and mood disorders,

paresthesia, palpitations, and pruritus. The observed signs of the disease included high body temperature, EM and multiple EM (MEM), heart rhythm disorders, myocarditis, pericarditis, encephalopathy, meningitis, encephalitis, cranial neuritis, radiculoneuritis, arthritis, myositis, and lymphadenopathy.

Based on the type of antibiotic and duration of its application, all patients who received antibiotic therapy were divided into three groups: those who were given benzathine benzylpenicillin once parenterally, those who were given antibiotics for seven days orally and those who were given antibiotics for 14 days orally (macrolides, tetracyclines, cephalosporins, semisynthetic penicillins). In each of these groups, those who suffered and those who did not suffer from the early stage of Lyme disease were singled out.

Data sources and examinations included biographical data from medical and health records, tick bite data, physical, radiological, and electrophysiological examinations, serological tests concerning Bb antigens (reaction of indirect immunofluorescence IIF or ELISA tests done at the Institute of Microbiology of the MMA) and specialist examinations according to indications.

The tick was removed either appropriately by a surgeon or an epidemiologist at the MMA, or inappropriately by the patients themselves and/or other adults when a child had been bitten. Tick gut contents were tested for the presence of Bb by an epidemiologist at the MMA Epidemiology Institute, in a dark field, using phase-contrast microscopy. All the patients were monitored clinically, laboratorially, and serologically within the period of one to 15 years.

Antibiotics registered for administration in our country and recommended for the treatment of Lyme disease were applied in the early antibiotic therapy.

Continuous variables were summarized as means (M) and standard deviations (SD); the significance between the groups was determined by the Student's t-test for the validity of data distribution. All variables were presented as frequency of certain categories, while statistical significance of differences was tested by the χ^2 test. Statistical significance was accepted at a minimum level of $p < 0.05$.

Principles of ICH Good Clinical Practice were strictly followed and ethical approval from the Ethics Committee was obtained on September 15, 2017.

RESULTS

In total, there were 2,070 patients. Group A consisted of 591 patients who received early antibiotic therapy, while Group B comprised 1,479 patients who did not receive any antibiotic therapy. Comparing the number of patients in the groups, a statistically significant difference was found due to the fact that Group B was significantly larger (Table 1) than Group A since early antibiotic therapy was applied only to those with a probable infection, according to the assessment of the responsible physician.

In both groups, there were more male patients, a total of 1,572 (75.94%), while there were only 498 females (24.06%), and there was no statistically significant difference

in the distribution of sexes in the groups. The average age of patients in Group A was 35.2 ± 19.4 years, while in Group B it was 39.4 ± 20.7 . The patients in Group B were statistically significantly older than those in Group A. The average age of women was 46.47 ± 20.26 years, while that of men was 33.89 ± 19.54 years, with women being statistically significantly older ($p = 0.001$).

When the presence of a tick during the examination is concerned, it was found that the distribution of the subjects was practically identical, as there was no statistically significant difference between these groups concerning the presence or absence of ticks, or the use of antibiotics ($p = 0.99$). The analysis of a large number of patients (2,041) with appropriately and inappropriately removed ticks showed a uniform ratio of these categories: 994:1047 (48.7%:51.3%) (Table 1).

The applied treatment was analyzed concerning the method of removing ticks. It was found that in Group B, which had not received early antibiotic therapy, the tick was removed appropriately in 652 patients (45%), inappropriately in 798 patients (55%), while 29 patients did not know about the tick bite and they came to the doctor's in the early phase of Lb. In Group A, the tick was removed appropriately in 342 patients (57.9%), and inappropriately

in 249 patients (42.1%). There were statistically significantly more patients in the group that had received the antibiotic and in which the tick was previously appropriately removed ($p < 0.001$).

The duration of tick presence ranged from one hour to more than 48 hours. By analyzing the duration of tick presence in the skin we can conclude that there was no statistically significant difference between the groups (Table 1).

After the tick bite in infected patients, the signs of Lb were most frequently present on the skin (Table 2).

The results show that the clinical signs on the skin were found in 31.51% of patients who did not receive early antibiotic therapy, as opposed to those who did (1.52%) ($p < 0.001$).

The total number of signs of the disease was 679, and the number of patients was 537, which means that in some patients there were several affected systems. Table 2 shows the frequency of signs on a particular organ system in relation to the total number of recorded signs in Group B (679). We observed that the nervous system was affected in 5.34%, other organs were affected in 3.49%, locomotor system in 2.84%, and cardiovascular system in 2.77% of the patients.

The frequency of changes on the skin, in relation to the total number of patients (547), was 86.84%, the changes

Table 1. Basic demographic and relevant clinical data

Parameters	Groups				Probability
	Early antibiotic treatment A		Without antibiotic treatment B		
	n	%	n	%	
Age (years), $x \pm SD$	35.2 ± 19.4		39.4 ± 20.7		$t = 4.24; p < 0.001$
Patient distribution (n = 2070)	591	24.06	1,479	75.94	$\chi^2 = 112.39; p < 0.001$
Sex					
male	457	77.3	1,115	75.4	$\chi^2 = 0.76; p = 0.38$
female	134	22.7	364	24.6	
Tick presence					
yes	260	44.0	652	44.1	$\chi^2 = 0.00; p = 0.99$
no	331	56.0	827	55.9	
Tick removal					
appropriately	342	57.9	652	45.0	$\chi^2 = 27.34; p < 0.001$
inappropriately	249	42.1	798	55.0	
Duration of tick presence (hours)*					
1–12	74	12.52	146	9.87	$\chi^2 = 2.31; p = 0.69$
13–23	228	38.58	562	38.00	
24–48	111	18.78	245	16.57	
> 48	63	10.66	157	10.62	
unknown	115	19.79	369	24.95	

*Skin, based on anamnestic data

Table 2. Clinical signs due to *Borrelia burgdorferi* exposure

Systems	Groups				Probability
	Early antibiotic treatment A		Without antibiotic treatment B		
	n	%	n	%	
Skin	9	1.52	466	31.51	$\chi^2 = 213.03; p < 0.001$
Nervous	0	0.00	79	5.34	Not shown due to extremely low frequencies in early antibiotic treatment group
Other	1	0.17	51	3.49	
Joints	0	0.00	42	2.84	
Heart	0	0.00	41	2.77	
Total	10	1.69	679	45.91	

Table 3. Efficacy of the early-applied antibiotic therapy

Antibiotics class	Lyme disease absent		Lyme disease present		Total	
	n	%	n	%	n	%
Macrolides	182	99.4	1	0.6	183	100
Semisynthetic penicillins	121	98.4	2	1.6	123	100
Benzathine benzylpenicillin	165	98.2	3	1.8	168	100
Tetracyclines	98	97	3	3	101	100
Cephalosporins	15	93.7*	1	6.3	16	100
Total	581	98.3	10	1.7	591	100

*significantly different ($p < 0.05$) from macrolides

Table 4. The frequency of the early phase of Lyme disease in patients regarding the type of treatment

Treatment	Lyme disease present		Lyme disease absent		Total	
	n	%	n	%	n	%
Early antibiotic treatment	10	1.7	581	98.3	591	100
Without antibiotic treatment	537	36.3	942	63.7	1479	100
Total	547		1523		2070	100
Probability	$\chi^2 = 258.40; p < 0.001$					

in the nervous system were registered in 14.44%, on other organs in 9.50%, on the locomotor system in 7.88%, and in the cardiovascular system in 7.49% of the patients.

At the same time, we observed that in patients who received early antibiotic therapy, there were no signs of disease in the nervous, cardiovascular, and bone-muscular systems.

After applying early antibiotic therapy in 591 patients, 581 (98.3%) of them did not develop the early phase of Lyme disease. Macrolides (99.4%) showed the highest efficacy, followed by semi-synthetic penicillins (98.4%), benzathine benzylpenicillin (98.2%), and tetracyclines (97%). Cephalosporins (93.7%) showed the lowest efficacy, which was statistically significantly lower in relation to other groups of antibiotics (Table 3).

In Group A, which had received early antibiotic treatment, only 10 (1.7%) out of 591 patients were infected, while 581 of them were not infected (98.3%). In contrast, in Group B, which had not received early antibiotic therapy, 537 (36.3%) out of 1,479 patients were infected, while 942 (63.7%) were not (Table 4). The difference found between these two groups of patients was highly statistically significant in favor of the group that had received early antibiotic therapy ($p < 0.001$).

DISCUSSION

Today, Lb is one of the greatest imitators in medicine, because it is a multisystem disorder involving many organs and systems, with the occurrence of a chronic disease form, the development of disabilities, autoimmune diseases, and sometimes lethal outcome [15].

The disease occurs in all parts of the world. In the United States, the incidence is 12–39 patients per 100,000, since the probable cases have also been reported since 2012 [16, 17].

In Europe, the incidence ranges from 35/100,000 patients in Germany to 206/100,000 patients in Slovenia [18].

In Serbia, the number of the infected is decreasing (6.83/100,000), since only 487 cases were reported in 2015 [19]. In the period from 1986 to 2000, Lb was represented in the zoonotic group with 16.34% in Belgrade, while 4,768 people developed the disease in Serbia from 1991 to 2000 [20].

In our study, there were significantly more males (75%), aged 11–30 years, as most of them were members of the army who had been outdoors in the field (younger ages were members of their families). In Europe, about 60% of women with a tick bite have been registered, which is similar to the findings in Serbia (57%), aged 20–60 years and over [19].

In the early 1990s, the infected ticks were frequent on the territory of Belgrade, ranging 20–67%, with a tendency to decrease. In 2007, this number amounted to 30% [2, 21].

The situation was similar everywhere. In Europe, the infection of *Ixodes ricinus* with Bb ranged 15–40%, in endemic areas of America up to 50%, while *Ixodes pacificus* was infected with Bb in 1–2% of cases [22]. The risk of the occurrence of manifest Lb after a bite by an infected tick in Europe ranges 1–4%, in hyperendemic areas 4.7–5%, but there are also data on a significantly higher risk (up to 27%) [4, 23, 24].

At the time of examination, 44% of our patients in both groups had a tick in the skin, while others came with a removed tick or not knowing about the bite. With the largest number of subjects, 48.31%, the tick stayed in the skin for up to 24 hours before the first examination.

In our study, there were 21 early-phase Lb patients with the tick staying in the skin for only 10 hours or up to one day who developed changes in the central and peripheral nervous systems, which is in agreement with some authors, but also in contradiction with some others [2, 3, 25, 26].

Given the large number of subjects in this study, i.e. 994 who had the tick removed appropriately (48.7%) and 1,047 who had it removed inappropriately (51.3%), it was possible to assess the significance of these two methods of tick removal for the occurrence of the disease. In the case of appropriate tick removal, the disease was reported in 22% of patients, while it was reported in 78% in the case of inappropriate removal, which was statistically significantly different. The ratio of patients with the tick inappropriately removed who were given early antibiotic therapy was 1.01% vs. 28.7% of patients in the group without antibiotic therapy. There was a significantly higher number of subjects in the group receiving the antibiotic and in whom the tick was previously appropriately removed ($p < 0.001$).

In patients with manifestations in the nervous and cardiovascular systems in our study, the tick was inappropriately removed in most cases, which is in line with the data given by Southern [27]. According to other authors' data concerning appropriate tick removal, the number of patients was statistically significantly lower in relation to the group where it was inappropriately removed (6% vs. 46%), but this study included a small number of subjects (52) [28]. According to the results of our authors, the early phase of Lb occurred in 0.61% of patients with appropriately removed tick, and in 2.5% of patients with inappropriately removed tick, while others claim that it occurred

in 0.2% of patients with appropriately removed tick and in 1.44% of patients with inappropriately removed tick [21, 29]. The aforementioned numerical indicators are lower in relation to the data from our research due to the longer monitoring of our patients and the timely started antibiotic therapy. The results of other studies suggest that 96% of patients with an appropriately removed tick did not suffer from Lb in a highly endemic region, thus emphasizing the importance of appropriate forceps tick removal even without the antibiotic prophylaxis [30, 31].

In our study, we observed the frequency of symptoms and signs of Lb and registered 12 different symptoms and 24 signs, which we grouped according to the affected organ systems. The disease was manifested on the skin in the form of EM and other skin changes in 86.84% of patients, in the nervous system in 14.44%, in other organs (lymphadenopathy, liver damage, high body temperature, hypothyroidism, multiple-systemic infectious disease syndrome – MSIDS) in 9.5%, on the locomotor system in 7.88%, and in the cardiovascular system in 7.49% of patients compared to the total number of patients (547). In patients who received early antibiotic therapy, there were no signs of disease in the nervous, cardiovascular, and musculoskeletal systems. In one patient (0.17%) who received early antibiotic therapy, we registered high body temperature without other signs of the early phase of Lb, as opposed to those who did not receive antibiotic therapy, in whom we registered the following: 3.49% MSIDS (in 29 patients), lymphadenopathy, liver, damage and hypothyroidism.

In patients who received early antibiotic therapy after a tick bite, Russian authors observed the infected (1.1%) without EM and with MSIDS, and in those without antibiotic therapy (12.3%) they noted those with MSIDS, sleep disorder, EM and MEM, lymphadenopathy, and cardiac disorders [32]. Other authors paid less attention to this category of patients and did not include them in the analysis when they evaluated the efficacy of prophylactic post-bite therapy [9, 14, 30, 33]. Our results show that in the group with antibiotic therapy only EM and MSIDS were observed, while all other signs were observed in the group without early antibiotic therapy. The difference between these two groups in relation to the number of signs was also statistically highly significant.

EM and MEM were significantly more frequently present (31.51%) in the group without early antibiotic therapy compared to patients with the treatment (1.52%). MEM was observed in 2.3% of patients without early antibiotic therapy, which was found in the United States in a higher percentage (20%) due to the early dissemination of Bb in that area [33]. Today, this can also be accounted for by new strains with high spirochetemia [34]. Compared to the total number of patients (547), the incidence of skin changes was 86.84%. Similar results were also reported worldwide, with 70–90% in the United States, and 48% in Slovenia [35]. Some patients with Lb without early antibiotic therapy had several organic systems affected, while 5.34% had changes in the nervous system, 2.47% in the locomotor system, and 2.77% in the cardiovascular system. Other studies state the same signs of disease with approximately equal frequency, which we also observed in our patients [31].

Unlike in our study, other authors followed their patients for a shorter period of time and observed fewer symptoms and signs. Among our patients, there were more neurological manifestations observed because we paid special attention to the damage of the peripheral nervous system due to Lb [36]. The incidence of cardiac manifestations in Lb was lower in relation to the data of other authors where they stated a frequency of up to 10% [37].

Opinions regarding the type and duration of antibiotic therapy in the treatment of Lb have not yet been harmonized. The general recommendation is that doxycycline, amoxicillin, and cefuroxime should be administered at an early phase for two to three weeks, while intravenous ceftriaxone, cefotaxime, or benzylpenicillin for two to four weeks in the case of extracutaneous manifestations [38, 39, 40]. The previous recommendation for treating the late phase was two to four weeks' therapy and even longer, until the disappearance of the symptoms [7]. New studies have not justified the extended, 12-week antibiotic treatment in late-stage patients with prolonged Lb symptoms [41]. Based on our experience, a longer four to six weeks' treatment prevents the dissemination of Bb and its affecting other organs and systems [1, 6, 8]. On the other hand, other authors consider that 10 days of doxycycline and amoxicillin therapy is efficient in the treatment of the early phase of Lb [42].

There is a significant difference in the recommendations for the treatment of the early phase of Lb, symptoms associated with Lb, and prophylaxis between the Infectious Diseases Society of America (IDSA) and the International Lyme and Associated Diseases Society, which advocates extended antibiotic treatment in all categories [8]. IDSA, along with several other medical associations, is in the process of developing new guidelines for the prevention, diagnosis, and treatment of Lb [43].

There are two opposing standpoints in the world regarding prophylaxis after a tick bite. The authors who are against the early application of antibiotic therapy base their opinion on a small proportion of instances of infection after a tick bite (2–3%), costs, and possible side effects of antibiotics [11, 12, 31]. Other authors, including us, advocate the use of early antibiotic therapy, regardless of the small number of infected persons after a tick bite. Among the infected, there are often patients with a severe clinical picture with extracutaneous manifestations and a possible fatal outcome [15].

In the prophylaxis of Lyme disease, the most commonly used drugs were cefotaxime, ampicillin, doxycycline, and penicillin [22, 33]. The results of a multicenter study in Germany and Austria show that the local application of 10% azithromycin at the site of a bite of an infected tick reduces the occurrence of EM [44]. We consider that the recommendation for local therapy is not justified because EM does not occur in 20–30% of infected patients, and patients later develop extracutaneous manifestations. It was previously described in experimental studies that the damage to the hematoencephalic barrier occurs as soon as 12 hours after spirochete inoculation, which does not support the use of local antibiotic therapy at the tick bite site [45].

In our study, we administered four groups of antibiotics orally and benzathine benzylpenicillin once parenterally in

order to prevent the disease after the tick bite. The results of our study show that early antibiotic therapy after the tick bite was very effective in the prevention of Lb. This was documented by a statistically significant decrease in the number of patients who received early antibiotic therapy (1.7%) compared to the group that did not receive this treatment (36.3%). Moreover, the symptoms and signs of the disease were also significantly less pronounced in the group with early antibiotic therapy compared to the group without it. Extracutaneous manifestations as an indicator of the severity of the clinical picture, in the group that received early antibiotic therapy, were not present at all. In contrast, in the group that did not receive early antibiotic therapy, symptoms and signs were observed in cardiovascular, nervous, and musculoskeletal systems.

The high incidence of early phase of Lb during the conducted trial at the MMA Clinic for Infectious and Tropical Diseases correlates with the highest number of Lb cases reported in Serbia in the period from 1991 to 2000, which totaled 4,768, and a high percentage of infected ticks [10, 20]. The aforementioned findings coincided with the great migration of the population due to sanctions and wars on the territory of former Yugoslavia. In addition, in our patients we observed a greater number of symptoms and signs than had been observed in other studies, as we followed the patients for more than one year [10].

A study by Russian authors showed that the use of doxycycline reduces the occurrence of the early phase of Lb in patients with the infected tick bite, as 11 times more patients were found in the group without prophylactic antibiotic therapy [32].

Several studies showed, according to the results of the meta analysis, that the disease did not develop in people who received prophylaxis 72 hours after the tick bite, and that the risk of developing the infection was 11 times lower in the group that received antibiotics (doxycycline or amoxicillin), compared to the placebo group (0.2%:2.22%) [14, 30].

The administration of a single dose of 200 mg doxycycline after a tick bite showed that early antibiotic therapy was very effective in reducing morbidity of the early phase of Lb, as the disease developed in eight times fewer patients compared to those who did not receive antibiotics (0.4%:3.2%) [9]. In this study, subjects were monitored for six weeks and only EM was described, which is insufficient to evaluate the efficacy of the drug, because symptoms and signs of the disease can be subsequently exhibited up to one year after the bite. EM does not occur in 20–40% of patients with early phase of Lb. Following the publication of the results of this study, a single dose of 200 mg doxycycline after the tick bite was recommended in certain individuals within the given treatment criteria [33].

Contradictory opinions concerning the justification of the application of antibiotics have existed since the discovery of Lb and its treatment up to the present [11, 12, 31]. According to some authors, a small number of patients after a tick bite (on average 1.1–3.4%) do not require the use of prophylactic therapy [11, 12, 31, 39]. In hyperendemic areas in the United States, Lb was developed in 3%

of patients with a tick bite without antibiotic therapy, so the use of prophylaxis in less endemic areas would have an even smaller effect [31]. In Europe, the tick infection rate is lower than in the United States, the risk of developing Lb is low (up to 4%), so prophylaxis is not recommended after the bite [4, 31].

This study showed that the early antibiotic therapy was extremely effective in preventing the disease compared to the control group (1.7%:36.3%). Our study followed the patients for 1–15 years, and therefore the percentage of patients who were infected at the early stage of Lb without early antibiotic therapy was greater [10]. Secondly, all five antibiotic groups were found to be clinically highly effective. The best results were achieved with roxithromycin (99.4%), followed by half-synthetic penicillins (98.4%), benzathine benzylpenicillin (98.2%), and doxycycline (97%), while cephalosporins (93.7%) showed the lowest statistically significant efficacy. As far as the efficacy of antibiotics and the duration of their use are concerned, (single-dose parenterally, seven or 14 days orally), there were no statistically significant differences.

Previously, the efficacy of short-term administration of amoxicillin as prophylaxis was not known and, therefore, was not recommended [33]. After a meta-analysis of four studies, it was concluded that the 10-day administration of amoxicillin may be as effective as 200 mg of doxycycline [30]. Our results showed that amoxicillin was very effective, even when given for only seven days. In addition, benzathine benzylpenicillin, not having been considered so far, also showed good efficacy.

Our study showed that, out of the 13 antibiotics we used, roxithromycin was the most effective one, but at the same time it was, by far, the most expensive drug. In previous studies, it was the second-line treatment for the early phase of Lb [33]. According to the principles of the World Health Organization that in the case of equal efficacy and good tolerance of more drugs, low-cost drugs should be used for treatment, in the past years we have decided to use ampicillin and doxycycline for a seven-day period. In case of need, i.e. in allergic patients (whom we did not register in our study), clarithromycin, azithromycin, (as suggested by British National Formulary [38]) or roxithromycin could be used.

In our study, we did not detect side effects of the applied drugs. There was no evidence of photosensitivity or gastrointestinal disturbances in soldiers who were exposed to the sun as part of their regular activities and diets that were not fully aligned with their usual family eating habits.

CONCLUSION

Taking into account our extensive experience in this field and results of the application of prophylactic therapies, we join the authors who are in favor of early antibiotic therapy after a tick bite. It is clinically justified, prevents the development of extracutaneous manifestations of Lb, is well tolerated, and the proposed antibiotics (doxycycline and ampicillin) are inexpensive.

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Утицај ране примене антибиотика на клиничке манифестације код оболелих у раној фази лајмске болести

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САЖЕТАК

Увод/Циљ Лајмска борелиоза (ЛБ) јесте мултисистемско инфективно обољење изазвано спирохетом *Borellia burgdorferi* (ББ) и настаје убодом инфицираног крпеља. Болест се испољава различито, а најчешће су захваћени кожа, зглобови, срце и нервни систем.

Циљ ове студије је био да се код особа код којих је дијагностикована рана фаза ЛБ утврди да ли постоје значајне разлике у испољавању симптома и знакова обољења између оболелих који су примили и оних који нису примили профилактичну, рану антибиотску терапију после убода крпеља.

Методе Испитивање је извршено на 2070 испитаника оба пола са убодом крпеља, лечених или прегледаних у Клиници у периоду 1989–2004. године. Испитаници су подељени у две групе – групу А ($n = 591$), која је примала рану, профилактичну антибиотску терапију, и групу Б ($n = 1479$), која ту терапију није примала. Рана антибиотска терапија подразумева примену антибиотика код особа са насталом инфекцијом вероватно до пет дана по убоду крпеља, а које нису имале

симптоме и знаке болести. Од антибиотика су примењивани цефалоспорини, макролиди, тетрациклини, полусинтетски пеницилини, понављано седам или четрнаест дана, или бензатин безилпеницилин једнократно.

Резултати Болест се развила код статистички значајно већег броја испитаника без профилаксе (537/1479) него код оних који су ту терапију примили (10/591), односно 36,3% : 1,7%. Применом пет група антибиотика закључено је да су за оптималну превенцију довољна само два: доксициклин и ампицилин у трајању од седам дана. Примењени антибиотици су испољили високу клиничку ефикасност, која се кретала од 93,7% (цефалоспорини) до 99,4% (макролиди) и била независна од дужине примене.

Закључак Примена ране антибиотске терапије после убода крпеља је ефикасна у превенцији ране фазе ЛБ, а када је болест била испољена, није било екстракутанних манифестација.

Кључне речи: лајмска болест; крпељ; антибиотици; профилакса