

Lyme borreliosis in Ivano-Frankivsk district, Ukraine: a epidemiological and clinical characteristics (2000-2022)

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ABSTRACT

Aim: To give epidemiological and clinical characteristics of the morbidity of Lyme borreliosis in Ivano-Frankivsk region for the period of 2000-2022 years.

Materials and Methods: There were used annual reports (form №1) from the State Institution "Ivano-Frankivsk Regional Center for Disease Control and Prevention of the Ministry of Health of Ukraine" and 200 of "Medical records of inpatients" (form 003/o) of the Ivano-Frankivsk Regional Clinical Infectious Diseases Hospital for 2000-2022 years.

Results: The morbidity of Lyme borreliosis in the Ivano-Frankivsk region has been permanently increasing since 2000. Natural foci have been identified, the number of which is increasing every year. There was noted late admission of patients to the Infectious Disease Hospital from the beginning of the disease, mainly at the stage of migratory annular erythema. There were almost no phenomena of intoxication and fever during the acute period. There were often observed the phenomena of hepatosis, joint damage and manifestations of the nervous system at the disseminated and chronic stages.

Conclusions: All landscape zones of Ivano-Frankivsk region are enzootic regarding Lyme borreliosis. Over the last 10 years in the region there is a tendency to a sharp increase of Lyme borreliosis morbidity. The clinical peculiarities of the disease in Ivano-Frankivsk region are: the absence of intoxication at the stage of migratory erythema, the phenomena of hepatosis. During the second and third stages of the disease there are polymorphic symptoms: recurrent erythema, damage of the retina, joints, liver, nervous system.

KEY WORDS: infectious diseases, ticks, natural foci, migratory erythema

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INTRODUCTION

Ixodic tick-borne Lyme borreliosis – is a polyetiologic zoonotic natural-focal infection in the group of spirochetoses with a transmissible mechanism of infection, characterized by polymorphism of clinical manifestations with the skin lesion, central and peripheral nervous system, heart, musculoskeletal system and predisposition to the prolonged and chronic recurrent course [1-4]. Over the last 20 years, many epidemiological and clinical studies of this disease have been performed in Europe, the United States and Ukraine [5-9].

The causative agent of Lyme borreliosis (LB) – is a gram-negative spirochete of the *Borrelia burgdorferi sensu lato* complex [10, 11]. The reservoir of the pathogen in nature – murine rodents, wild and domestic animals, as well as birds. *Borrelia* is transmitted to humans through the bites of ixodic ticks: *I. ricinus* and *I. persulcatus*. The geographical distribution of LB is similar to natural habitat of other tick-borne infections (tick-borne encephalitis, human granular anaplasmosis, babesiosis)

[11]. With the saliva of the tick, the pathogen enters the human body, causing both a local reaction (annular erythema) and damage of the internal organs due to dissemination by lymphatic and hematogenous routes. The development of autoimmune reactions and the possibility of long-term intracellular persistence of the pathogen are the main causes of infection chronization [12-15].

Improved diagnosis of LB: serological tests using enzyme-linked immunosorbent assay, immunoblotting, detection of *Borrelia* DNA by PCR-based diagnostics. However, clinical symptoms are the leading ones in the diagnosis of LB [16, 17].

The intensity of the epidemic process and clinical peculiarities of LB course differ in various regions of the world and in regions of Ukraine [18-22], thus the observational study of local epidemiological and clinical peculiarities of LB in Ivano-Frankivsk region is important and counts for development of preventive and curative measures.

AIM

To give epidemiological and clinical characteristics of the morbidity of Lyme borreliosis in Ivano-Frankivsk region for the period of 2000-2022 years.

MATERIALS AND METHODS

There were used annual reports (form №1) from the State Institution "Ivano-Frankivsk Regional Center for Disease Control and Prevention of the Ministry of Health of Ukraine" and 200 of "Medical records of inpatients" (form 003/o) of the Ivano-Frankivsk Regional Clinical Infectious Diseases Hospital for 2000-2022 years.

The diagnosis was confirmed (until 2013) by the method of indirect immunofluorescence (IIFT), then using enzyme-linked immunosorbent assay (ELISA) there were revealed antibodies IgM, IgG to the complex *Borrelia burgdorferi sensu lato*. Since 2014, the method of immunoblotting with the detection of IgM, IgG to antigens *Borrelia burgdorferi sensu stristo*, *Borrelia garinii*, *Borrelia afzelii* was also used.

Statistical analysis of data was performed using the Microsoft Excel Statistical Package for Microsoft 365 MSO (setup 2311 of version 16.0.17029.20068) (32-bit version). License ID: EWW_58cc64b2-cc32-48b6-bd4b-cce379e20247_574357c00167ce3139.

The results obtained during the research are represented in the form of absolute numbers (quantity

of registered LB case in a particular year), rates (LB morbidity in a particular year), proportions with errors and confidence intervals (for the analysis of categorical data: part of patients with different clinical symptoms among all patients) and average values and their errors (for the analysis of quantitative data). The values were calculated according to standard formulas. To determine the long-term trend (growth, stabilization, decrease) we were used the analysis of dynamic series calculated according to standard formulas (absolute change, percentage change, relative change, percentage change from baseline, moving average). For graphic presentation of phenomena development, we used trend lines in Microsoft Excel programme.

RESULTS

Ivano-Frankivsk region is located in the West of Ukraine and borders with Lviv, Ternopil, Chernivtsi and Zakarpattia. Prykarpattia covers three different landscape zones: Prydnistrovya or forest-steppe, Peredhirya with forest-meadow landscapes, the South-west of the region is represented by the flanks of the Eastern Carpathians, covered with continuous deciduous and coniferous forests. The region is located in zone of the temperate continental climate. The peculiarity of the Ivano-Frankivsk region is determined by its physical-geographical location, favorable weather condi-

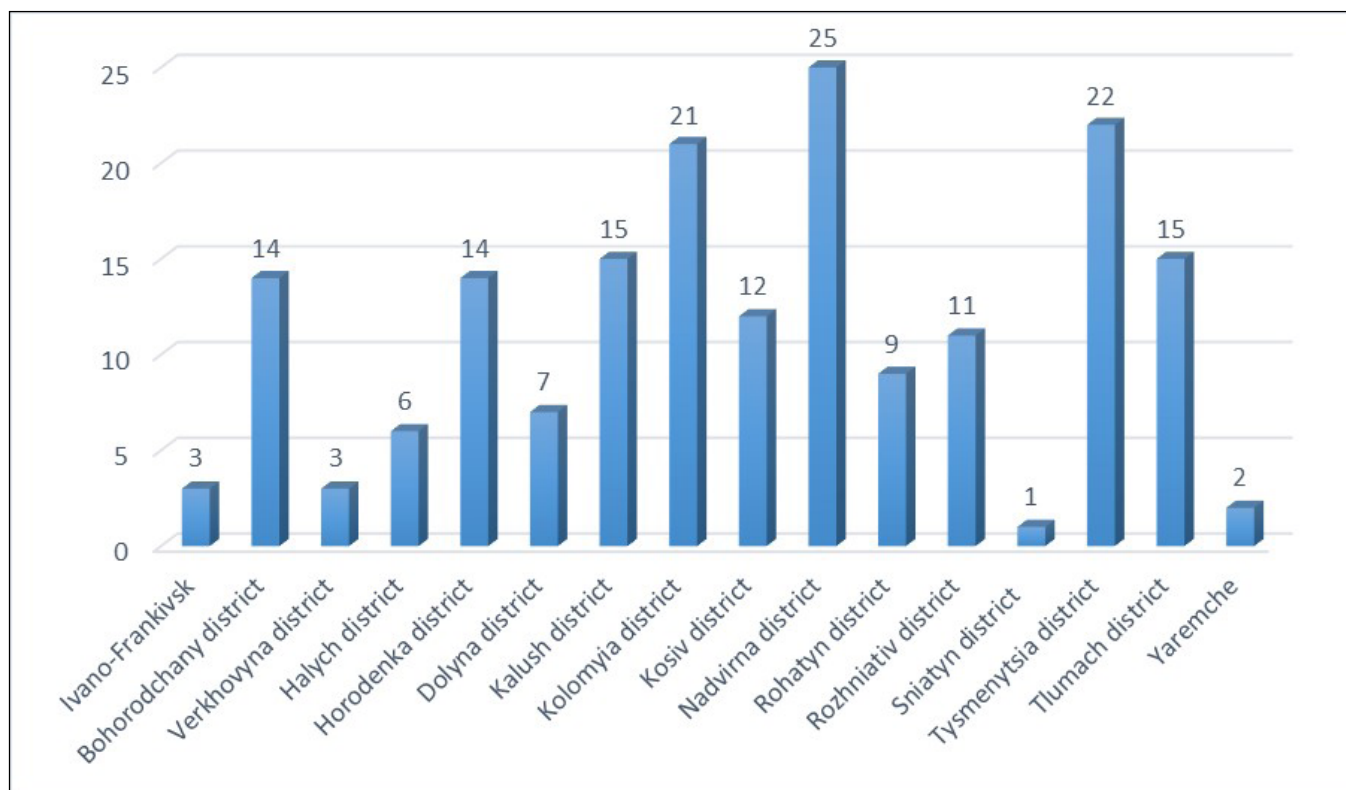


Fig. 1. The number of foci of Lyme borreliosis in administrative districts of the Ivano-Frankivsk region in 2022.

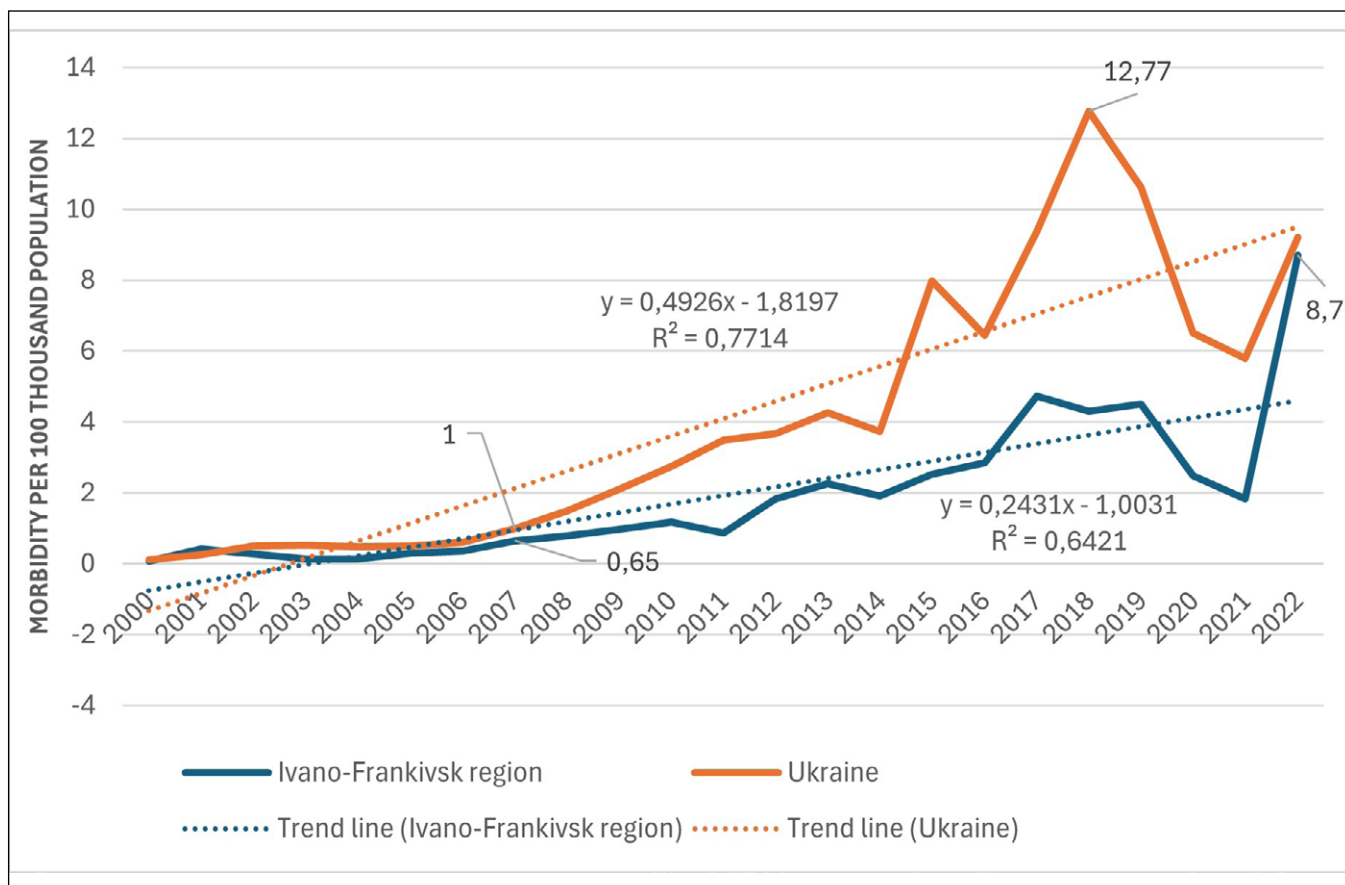


Fig. 2. Dynamics of Lyme borreliosis morbidity in Ivano-Frankivsk region and in Ukraine.

tions and composition of the fauna, which provides the prerequisites for the formation of the natural and anthropurgic foci of infectious diseases [23, 24].

Enzootic territories have been identified concerning LB in Prykarpattia: in the environs of the regional center (city and suburban villages), as well as in Prydnistrovya (Halych, Kalush, Tysmenytsia, Tlumach, Rohatyn, Horodenka districts), in Peredhirya (Bohorodchany, Dolyna, Kolomyia districts), and in the mountaneous – Kosiv and Nadvirna districts (Fig. 1).

In 2022, the number of foci has reached 199. The largest number of foci was observed in Nadvirna district, a large number was also noted in Kolomyia and Tysmenytsia districts.

To determine the layer of seropositive population in different districts of the region, there were taken blood samples in a healthy population. The study was performed on the basis of the Lviv Research Institute of Natural Focal Infections. It was found that on average $13.1 \pm 2.2\%$ of the studied healthy individuals of Nadvirna, $31.3 \pm 3.1\%$ – of Dolyna, $20.0 \pm 2,6\%$ – of Halych, $11.4 \pm 2.1\%$ – of Kolomyia, $26.2 \pm 2.9\%$ – of Sniatyn, $42.3 \pm 3.3\%$ – of Kalush districts, $14.1 \pm 2.3\%$ – of Ivano-Frankivsk have antibodies to *Borrelia burgdorferi* (IgG, IgM). Field material (ticks) was also collected.

The level of infection of ticks with *Borrelia* has reached $25.0 \pm 2.9\%$.

The morbidity (incidence) of LB since 2000 to 2022 both in Ukraine and in the region is constantly increasing. At the same time, over the last 10 years we observed significant increasing of morbidity in Ivano-Frankivsk and in Ukraine. The dynamics of the incidence of LB in Ivano-Frankivsk region and in Ukraine (2000 - 2022) is represented in Fig. 2.

According to the chart, the period since 2000 to 2007 differs in small fluctuations in morbidity, and in the indices of 0.07 per 100 thousand of population (Ivano-Frankivsk region) and 0.12 (Ukraine) have reached – 0.65 and 1.0, respectively. Intensive growth in morbidity has occurred over the past 10 years. In 2018 in Ukraine this index has increased in comparison with 2000, 100-fold (12.77 per 100 thousand of population), in Ivano-Frankivsk region the highest index was in 2022 – 8.7 that is 124 times higher, then in 2000. Over the last 10 years, 360 patients have been registered in Ivano-Frankivsk region.

According to the research aim, we also analysed dynamic of Lyme borreliosis cases in Ivano-Frankivsk region and Ukraine for the period of 2000-2022 years. Main parameters of dynamic series are presented in Table 1 and Table 2.

Table 1. Lyme borreliosis cases in the Ivano-Frankivsk region dynamic (Indicators of dynamic series analysis)

Year	LB, cases	Absolute change	Percentage Change	Relative Change	Percentage Change from baseline	Moving average
2000	1	-	-	-	100,00	-
2001	6	5,00	600,00	500,00	500,00	3,67
2002	4	-2,00	66,67	-33,33	300,00	4,00
2003	2	-2,00	50,00	-50,00	100,00	2,67
2004	2	0,00	100,00	0,00	100,00	2,67
2005	4	2,00	200,00	100,00	300,00	3,67
2006	5	1,00	125,00	25,00	400,00	6,00
2007	9	4,00	180,00	80,00	800,00	8,33
2008	11	2,00	122,22	22,22	1000,00	11,00
2009	13	2,00	118,18	18,18	1200,00	13,33
2010	16	3,00	123,08	23,08	1500,00	13,67
2011	12	-4,00	75,00	-25,00	1100,00	17,67
2012	25	13,00	208,33	108,33	2400,00	22,33
2013	30	5,00	120,00	20,00	2900,00	27,00
2014	26	-4,00	86,67	-13,33	2500,00	30,00
2015	34	8,00	130,77	30,77	3300,00	32,67
2016	38	4,00	111,76	11,76	3700,00	45,33
2017	64	26,00	168,42	68,42	6300,00	53,33
2018	58	-6,00	90,63	-9,38	5700,00	61,00
2019	61	3,00	105,17	5,17	6000,00	51,00
2020	34	-27,00	55,74	-44,26	3300,00	40,00
2021	25	-9,00	73,53	-26,47	2400,00	59,67
2022	120	95,00	480,00	380,00	11900,00	-

Moving average represent clear increasing tendency of LB both in Ivano-Frankivsk region and in Ukraine. For absolute change there is some fluctuation (decreasing in some years), but mostly we observed phenomena increasing (Table 1, Table 2). The same tendency is typical for percentage change and relative change, there for percentage change from baseline especially during last 10 years increase extremely.

There analysed 200 medical records of patients with LB who have been treated in the Ivano-Frankivsk Regional Clinical Infectious Diseases Hospital since 2000 till 2022.

The largest number of people seeking medical attention due to tick suction, was registered in May-June, the second wave was observed in September-October. Women predominated among the patients – 108 (54.0±3.5%), children were 24 (12.0±2.5%). The incubation period lasted from 1 week to 3.5 months, on average 28.7±1.9 days. Half of the patients – were urban dwellers who visited the forest in the summer or worked in country houses near the forest. Patients were admitted to the hospital, mainly in the autumn-winter period and even the next year spring, i.e. after 1.5 - 3

months and more since the onset of the disease, often in January, chronic forms even more than after 1 year. In most patients, the diagnosis of LB was determined in the early localized stage of migratory annular erythema – 142 (71.0±3.2%), in the second disseminated stage – in 30 (15.0±2.5%), in the third stage of persistent infection – in 24 (12.0±2.3%), in non-erythematous form – in 4 (2.0±0.9%) of patients.

Migratory annular erythema was observed during the first localized stage. The duration of erythema lasted from 2 weeks to 2.5 months, with an average of 53.1±4.2 days. The size of the erythema in diameter averaged 17.8±2.4 cm. Body temperature increased in 12 patients (8.22±1.9%) to subfebrile figures within 3-4 days. In 15 (10,27±2.15%) of patients at this stage, the liver size has increased, and ultrasound showed the signs of hepatosis. Some patients had had: headache, joint pain, heart pain, dizziness and others (Table 3).

During the second disseminated stage, cyanotic hyperpigmentation, the presence of additional spots, vesicles, as well as weakness, fever, headache, joint and muscle pain were observed at the site of fading erythema. There were 5 (16.67±2.64%) of patients who

Table 2. Lyme borreliosis cases in Ukraine dynamic (Indicators of dynamic series analysis)

Year	LB, cases	Absolute change	Percentage Change	Relative Change	Percentage Change from baseline	Moving average
2000	59	-	-	-	100,00	-
2001	122	63,00	206,78	106,78	106,78	141,00
2002	242	120,00	198,36	98,36	310,17	202,33
2003	243	1,00	100,41	0,41	311,86	238,00
2004	229	-14,00	94,24	-5,76	288,14	236,00
2005	236	7,00	103,06	3,06	300,00	249,00
2006	282	46,00	119,49	19,49	377,97	328,00
2007	466	184,00	165,25	65,25	689,83	479,67
2008	691	225,00	148,28	48,28	1071,19	708,67
2009	969	278,00	140,23	40,23	1542,37	974,67
2010	1264	295,00	130,44	30,44	2042,37	1277,00
2011	1598	334,00	126,42	26,42	2608,47	1512,33
2012	1675	77,00	104,82	4,82	2738,98	1736,33
2013	1936	261,00	115,58	15,58	3181,36	1767,00
2014	1690	-246,00	87,29	-12,71	2764,41	2350,67
2015	3426	1736,00	202,72	102,72	5706,78	2624,67
2016	2758	-668,00	80,50	-19,50	4574,58	3360,00
2017	3896	1138,00	141,26	41,26	6503,39	4022,00
2018	5412	1516,00	138,91	38,91	9072,88	4596,67
2019	4482	-930,00	82,82	-17,18	7496,61	4213,00
2020	2745	-1737,00	61,24	-38,76	4552,54	3223,00
2021	2442	-303,00	88,96	-11,04	4038,98	3020,67
2022	3875	1433,00	158,68	58,68	6467,80	-

had hepatitis, 3 patients (10.0±2.12%) had retinal angiopathy (spasm and sclerosis).

During the third persistent stage, the recurrent erythema persisted, sometimes up to 18 months; there were weakness, dizziness, enlargement of regional lymph nodes to the site of the tick bite up to 1.5-2 cm, joint damage – 3 (12,5±2.34%): swelling and pain (synovitis of the knee, talocrural, radiocarpal and other joints), decreased visual acuity, retinal angiopathy – 9 (37,5±3.42%), hepatitis. Rarely there were observed changes in the cardiovascular system: palpitations, pain in the heart area, systolic murmur at the apex.

There were manifestations of the nervous system at different stages of the disease in 48 (24.0±2.82%) of patients: serous meningoencephalitis 4 (2.0±0.92%), peripheral neuritis of the VII pair of the trigeminal nerve – 3 (1,3±0.75%), the phenomena of encephalomyelitis and polyneuropathy – 21 (9.13±1.90%) (vestibulo-ataxic syndrome, weakening of convergence, decreased photoreaction, Marinescu-Rodowicz's symptom, rocking in Romberg's position, eyelid tremor, diplopia), other patients had had: headache, dizziness, hearing loss, tinnitus.

Almost all patients were determined a mild form of anemia (Hb – 98.7±6.3 g/l), lymphocytosis (42.4±3.3%). In 26 patients (13.0±2.22%) there was hypoalbuminemia with the increased level of gamma-globulins (from 28.0 to 43.0%).

DISCUSSION

Long-term monitoring of LB in Ivano-Frankivsk region has shown a significant increase of morbidity over the last 10 years. Similar data are published by researchers from other European countries [25, 26]. Although in general the incidence in the region is lower than in Ukraine, but this creates a problem in terms of public health, as the actual number of patients is much higher [19]. That is also pointed out by several researchers from other countries [18, 20]. The decrease in the number of registered patients with LB in 2020-2021 years can be explained by the impact of anti-epidemic measures in case of coronavirus disease COVID-19 on population activity. Serological examination of the healthy population

Table 3. Characteristics of clinical symptoms in patients with Lyme borreliosis (first localized stage), N=146


Symptoms	Number of Patients	%	±m	95 % Confidence Interval Lower limit	95 % Confidence Interval Upper limit
Weakness	26	17,81	3,17	11,60	24,01
Fever	37	25,34	3,60	18,29	32,40
Increasing body temperature up to 38°C	12	8,22	2,27	3,76	12,67
Headache	31	21,23	3,38	14,60	27,87
Dizziness	11	7,53	2,18	3,25	11,82
Nausea	7	4,79	1,77	1,33	8,26
Catarrhal signs (sore throat, dry cough, runny nose)	12	8,22	2,27	3,76	12,67
Muscle pain	9	6,16	1,99	2,26	10,07
Neck muscle stiffness	5	3,42	1,51	0,47	6,37
Joint pain	14	9,59	2,44	4,81	14,37
Heart pain	8	5,48	1,88	1,79	9,17
Regional lymphadenitis	24	16,44	3,07	10,43	22,45
General lymphadenopathy	3	2,05	1,17	-0,25	4,36
Benign lymphocytoma of the skin	5	3,42	1,51	0,47	6,37
Hepatomegaly	15	10,27	2,51	5,35	15,20
Splenomegaly	7	4,79	1,77	1,33	8,26
Migratory annular erythema	142	97,26	1,35	94,61	991

revealed a high percentage of antibodies to *Borrelia* in almost all areas of the Ivano-Frankivsk region. These data are correlated with the authors' one on the results of a serological examination of the sera of patients from Western Ukraine [19]. The formation of new enzootic foci is associated with an increase of tick infection, favorable natural factors in the region and the lack of preventive measures. This conclusion is also consistent with the data of some authors [25, 26]. Absence of the expressed intoxication, increase in body temperature in the acute period cause late hospitalization of patients and administration of etiotropic therapy. Polymorphism of clinical manifestations during the second and third stages of the disease, the variability of laboratory studies' results create difficulties in the diagnosis of Lyme borreliosis [12, 22]. It should be based on a complex of epidemiological (the fact of ticks' sucking, being in an endemic zone in the seasonal period) and characteristic clinical data (the presence of erythema, joint damage, neurological symptoms). This is consistent with the data [19, 26].

CONCLUSIONS

1. All landscape zones of Ivano-Frankivsk region are enzootic regarding the Lyme borreliosis, seropositive healthy population in different areas of the region is from $11.4 \pm 2.1\%$ to $42.3 \pm 3.3\%$.
2. Over the last 10 years in the region there is a tendency to a sharp increase of the morbidity of Lyme borreliosis, since 2000 – it has increased 124-fold.
3. $71.0 \pm 3.2\%$ of patients are admitted to the infectious hospital in the stage of migratory erythema, without of intoxication, with short-term rise in subfebrile temperature in $8.22 \pm 1.9\%$, the phenomena of hepatosis in $10.27 \pm 2.15\%$ of patients.
4. During the second and third stages of the disease there are polymorphic symptoms: recurrent erythema, a significant frequency of retinal vascular lesions – up to $37.5 \pm 3.42\%$, joints – $12.5 \pm 2.34\%$, liver – $16.67 \pm 2.64\%$.
5. Neuroborreliosis occurs in $24.0 \pm 2.82\%$ of patients at different stages of the disease: serous meningoencephalitis, peripheral neuritis with facial nerve paresis, the phenomena of encephalomyelitis and polyneuropathy.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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