

REVIEW PAPER

LYME Disease: Prevention and Treatment of Recurrent Disease

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Abstract

Introduction: Lyme disease is a multisystem infectious disease caused by the spirochete *Borrelia burgdorferi* and transmitted via tick bite.

Aim: This study aims to draw the attention of health professionals and the community about the preventive measures and treatment of Lyme disease.

Methods: Extensive literature search in the electronic database "Pubmed", "Google Scholar", the website of the center for Disease Control and Prevention (CDC) and in scientific journals via search engine with the keywords: Lyme disease, symptoms, removal, treatment. There was a time restriction, the last ten years. A key criterion for the selection of articles was English language.

Results: Lyme disease is the most common disease transmitted by ticks in many countries. If not treated immediately may cause serious complications. The diagnosis is based primarily on the presence of erythema migrans, characteristic of the disease. Listed events in the skin, musculoskeletal and central nervous system. The treatment is simple and involves antibiotic therapy. However, a proportion of patients may develop most-treatment Lyme disease syndrome, which makes treatment difficult. Finally, it occurs more frequently in children and in young adults living in rural areas.

Conclusions: Because of the increase of incidents of Lyme disease in many countries of the world, it is vital that the mobilization of both, health professionals and the community to prevent and deal with it. Moreover, deemed necessary and further investigation of the phenomenon.

Key Words: Lyme disease, prevention, removal, symptoms, treatment

Introduction

Infectious or contagious diseases are caused by living organisms potentially pathogenic or mandatory, as well as the toxic products. While there has been some progress with regard to the prevention and treatment of infectious diseases, however, important causes of morbidity and mortality remain in many countries (Friis & Sellers, 2008).

A serious infectious disease is Lyme disease or Lyme Borreliosis, which according to studies is endemic or recurs even today in many parts of the world. Among the areas it

is located is Europe, while in Greece the disease is rare, the actual impact is unknown. Lyme disease is described as a disease entity first time in the USA, while manifestations were reported decades earlier in Europe (Szczepanski & Benach, 1991). It is the most frequently reported infectious disease in the USA, and more than 20,000 cases reported annually worldwide (CDC, 2014; CDC, 2014). In 2012 in Pennsylvania reported 4,146 confirmed cases per 100,000 population in New Jersey 2.732 and Massachusetts 3.396. The number of confirmed and probable cases of Lyme

disease reported to the Center for Disease Control and Prevention (CDC) in 2011 increased by 2,939 (9.7%) compared with 2010. Nevertheless, the total number of cases remained significantly lower than in 2008 and 2009 (Marques, 2010). Between 2008 and 2009 there was a 3.6% increase in confirmed cases and 35.6% increase impossible cases (CDC, 2011).

Epidemiology

Lyme disease is the most common disease transmitted by arthropods in America. 2012 was the seventh most common notifiable disease at national level, although it is stated that it mainly occurs in the northwestern regions of the United States (Figure 1). The cases arriving in the USA from 17.029 in 2001 to 24.364 for 2011 (CDC, 2014 ; Stanek et al, 2012). From 1992 to 2006, the number of cases of Lyme disease reported of this CDC increased from 9.908 cases per year to 19.931 cases per year (CDC, 1995). Also the number of established endemic areas in Canada has increased recently (CDC, 2014; CDC, 2014). Other areas where the disease is endemic are northeastern, Central Atlantic, Central and North America and northern California (American College of Rheumatology, 2008). In Europe, cases outbreaks have been reported in Germany, Austria, Switzerland, France and Sweden, while in Greece the disease is rare. The annual incidence is reported to be 14-140 per 100.000 inhabitants in Europe vary widely from region to region. In Greece the presence of *Ixodes ricinus* is known from studies of the 1980s in the regions of Macedonia and Thrace, but also in areas of southern Greece, where the humidity is lower and the temperature is higher. In a study in Greece it was found that 45% of ticks collected in 11 countries in Northern Greece, is the *Ixodes ricinus* that causes Lyme disease (Papa et al, 2008).

Literature Review of Studies

According to the guidelines of the Infectious Diseases Society of America (IDSA), the ME as a clinical manifestation is enough to diagnose the Lyme disease, without confirmation by further laboratory tests to be required and it is a characteristic clinical sign for the diagnosis of the disease (Wormser et

al, 2006). However, there was a study in which doctors did not detect it in all patients who were infected by the bacterium *Borrelia burgdorferi*, as they compared it to many other complications, such as cellulitis from other diseases (Wormser et al, 2008). A series of conditions resemble the ME. Nevertheless, the rapid and sustained expansion of lupus damage is unique for ME of Lyme disease (Tibbles & Edlow, 2007). In a study it was also found that physicians of primary care in an endemic area with Lyme disease in France correctly identified the migratory erythema only in 72 percent of patients (Lipsker et al, 2004).

Prevention of Lyme disease is very important especially for people at high risk (park rangers and hikers). Avoiding areas with high burden of ticks (wooded areas or areas which are rich in vegetation and have large population of deer) is the best preventive measure. A case-control study in an endemic area in 2009 concluded that the realization of the presence of ticks within 36 hours and having a bath within two hours can reduce the risk of infection.

The objective of a recent study was to determine the most appropriate protective behaviors and promote them in order to protect members of the public from the Lyme disease, identify drivers and barriers for this behavior, and determine the strongest predictors of hers (Mowbray et al, 2014). Samples of patients appear to be incubated via a two step pre-enrichment procedure, followed by immunostaining with or without the polymerase chain reaction (PCR). However, this was revised in a study creating serious concerns regarding the false positive results caused by laboratory contamination and possible misdiagnosis (Nelson et al, 2014). According to another study, out of 61% of patients diagnosed with early Lyme disease, 13% did not show the ME. Of those who did not have ME, 54% had previously been misdiagnosed. Among those who developed a rash, the diagnose of it initially got missed in 23% of patients to whom it was confirmed in the end. Of all patients who were previously misdiagnosed, 41% had received antibiotic treatment which is likely to be ineffective against Lyme disease (Aucott et al, 2009).

Moreover, a relevant study from the Netherlands has used an approach that provides information about tick bites and Lyme disease in the general Dutch population. In this study, a slight qualitative approach is presented to identify high risk groups and the conduct of in-depth interviews in order to create a profile about risk groups depending on their characteristics (Beaujean et al, 2013).

Information on the epidemiology of *Ixodes ricinus* in Greece is limited. The first evidence of infection on a human was reported during the course of an investigation on the etiology of epidemic dengue in 1927-1928 (Papa et al, 2008). Within this research antibodies to *Ixodes ricinus* were detected by hemagglutination (Theiler et al, 1960). Another serological study which was performed on animals that live permanently in Northern Greece, showed that 16.8% of goats, 5.6% of pigs, 4.7% of horses, 5.1% of sheep and 3.1% of bovine had antibodies against *Ixodes ricinus* (Antoniadis et al, 1990). In the latest study conducted for the presence of antibodies against *Ixodes*, the prefecture of Halkidiki was the one with the highest prevalence (Pavlidou et al, 2007).

In most cases, the early stages of Lyme disease patients recover rapidly and completely with appropriate antibiotics orally. Antibiotics which are commonly used for (oral) treatment per os (not sure about this one) include doxycycline, amoxicillin or cefuroxime. Also studies indicate that owing to the frequent allergies of doxycycline derivatives of penicillin and azithromycin can be used. Many other supporters, who found that azithromycin is as effective for the treatment of early Lyme disease, also agree on these studies (Massarotti et al, 1992). Of course, others argue that azithromycin is inferior when compared with amoxicillin (Luft et al, 1996).

According to researchers on the post Lyme disease syndrome or arthritis that does not respond to antibiotic treatment has been a latent intracellular infection that may require months or years of antibiotic therapy to eradicate the pathogen. 21 Critics of this position suggest that continued symptoms can be explained by an autoimmune reaction

caused by a connection between Lyme disease and certain human leukocyte antigens, 16, 17 and 21. Although there is controversy about the post Lyme disease syndrome and chronic treatment of Lyme disease, four randomized clinical trials found no evidence to suggest that prolonged antibiotic therapy is beneficial (Klempner et al, 2001; Krupp et al, 2003). Patients without clinical signs of classical Lyme disease, but with chronic fatigue, arthralgias and myalgias do not respond to antibiotics, even if multiple treatments are provided to them. This is supported by many scholars who conclude that serological tests can reliably rule out Lyme disease in patients with these chronic symptoms, thus avoiding unnecessary treatment with antibiotics (Fawcett et al, 1977). For the majority of patients with post-Lyme disease syndrome, differential diagnosis should be considered. This avoids the long-term side effects of antibiotic treatment.

Furthermore, the American Academy of Pediatrics, the American Academy of Neurology and the American College of Rheumatology do not recommend prolonged antibiotic therapy in post-Lyme disease syndrome (Wormser et al, 2006; Marques, 2008). Moreover, a recent survey found that 97% of primary care physicians in endemic areas with Lyme disease did not diagnose or treat patients with post-Lyme disease syndrome (Johnson & Feder, 2010).

The aim of this literature study is to inform and raise awareness among health professionals about the causative factors, pathogenesis, symptomatology, epidemiology, diagnosis and treatment of Lyme disease, given the need to update knowledge of infectious diseases that they may have to face within a multicultural approach of patients.

Methodology

The search of the resources of this literature review was primarily conducted on the internet. We used the following scientific databases: Pubmed, Google Scholar and the site of the Center for Disease Control and Prevention (CDC). The content of the articles was related to Lyme disease and more specifically to the pathogenesis,

clinical picture, diagnosis, treatment and prevention. Also, statistical and epidemiological data regarding it was sought. These articles were scientific reviews and epidemiological studies. Another basic criterion in the selection of articles was the English language, because not enough scientific studies and research have been conducted in the Greek language yet. The key-phrases that were used were as follows: Lyme disease, Lyme symptoms, Lyme prevention, Lyme treatment. Exclusion criteria of articles were languages other than English, and articles that do not allow access to the full text. Totally 80 articles were found, 30 of which were excluded because they did not have the full text and another 8 because they were in another language. Finally, 42 articles were included in the study.

Results

Pathogenesis-Clinical Signs and Symptoms

Lyme disease is caused by the bacterium *Borrelia burgdorferi*, which was recognized in 1982, when it was isolated by Burgdorferi and Barbour. The factor that causes the Lyme disease is the spirochete from the complex *Borrelia burgdorferi*. This complex contains at least 12 species. The transmission takes place (happens) through the bite by the saliva and feces of ticks (Tilly & Stewart, 2008). These microbes have thin elongated body and they are predominantly found on ticks, mosquitoes and flies and through these the disease is transmitted to humans. The most pathogenic tick is a hard tick that occurs in deer and the «*Ixodes ricinus*» (Halperin et al, 2012). Ticks may use as a host mammals, birds, reptiles, and amphibians. They should also have a new host at every stage of their lives. In most cases, the tick must adhere to the skin for 36 to 48 hours or more before the microbe of the disease gets transmitted (CDC, 2014). Then, the bacteria enter the blood and migrate to various tissues and organs. After an incubation period of 30 days, having escaped the defense mechanisms of the organism, it migrates distal skin and occurs with a lesion called erythema migrans. Thus, effects are manifested in the skin, joints, heart and nervous system. (Halperin, 2014).

Early localized stage (3-30 days after being bitten by a tick)

It appears with clinical signs and symptoms on the skin, the heart, the musculoskeletal and central nervous system. This stage, which includes local infection manifests with flu-like symptoms and a rash, and begins with the bite of a tick. Some of the signs and symptoms, the most important of whom is red, expanding rash called erythema migrans (ME), are fatigue, rigors, fever, headache, myalgias and arthralgias, swelling of the lymph nodes and the stiffness of the neck. Also, some people appear mild swelling or redness at the point of the tick's bite, which subsides in 1-2 days (like a mosquito bite). This does not mean that these people suffer from the Lyme's disease. Often, these symptoms coexist with ME. The ME starts from the point of the tick's bite with highlights (main areas of manifestation in) of appearance the axilla, groin and thigh. It extends over several days to 30 cm across. It is warm to touch and rarely painful or itchy. Finally, the ME may leave scars anywhere in the body. (Allen et al, 2004).

Early diffuse stage (days to weeks after the tick bite)

The second stage is characterized by disseminated infection. Without treatment, the infection is likely to spread to other parts of the body beyond the point of the bite, causing a number of symptoms that can appear and disappear. These are the additional distortions, the ME in other areas of the body, the personal or paralysis of Bell (loss of muscle tone in one or both sides of the face), nausea, severe headaches, cervical usually stiffness due to meningitis (inflammation of the spinal cord), pain and swelling in large joints (knees) often cause the so-called "Lyme arthritis", severe pain that may influence sleep, heart palpitations and dizziness owing to changes in heartbeat, hepatitis, swollen testicles and splenomegaly. Many of these symptoms will be resolved in a few weeks or even months without treatment. However, the lack of treatment may lead to additional complications which are described below. Finally, it is worth noting that during this stage, non-protective antibodies begin to grow (Allen et al, 2004).

Crude diffuse stage (months to years after the tick bite)

After the second stage, bacterium borrelia survives locally for some time with few or no symptoms and a long latency period may mediate. The third stage is characterized by persistent disease that begins 2 to 3 years after the initial bite, and it constitutes the chronic form of the disease with persistent clinical manifestations, especially joints, nervous system, and skin. Almost 60% of patients with infection which is not treated may develop intermittent bouts of arthritis, with severe pain primarily in large joints (especially knees) and swelling. Some of the neurological manifestations are numbness or tingling in the arms or legs, severe pain and problems with short-term memory (Steere et al, 1987; Auwaerter et al, 2004).

Symptoms that persist after treatment (post treatment syndrome of Lyme disease (PTLDS)

About 10-20% of patients with Lyme disease symptoms last for months to years after the antibiotic treatment. Some of them are sleep disturbances, cognitive deficiencies, fatigue, pain in muscles and joints. According to indications PTLDS is caused by an autoimmune response in which the immune system of an individual does not stop responding, thus damaging the tissues of the body, even after the infection has been cleared (Marques, 2008).

Complications

If the disease is left untreated there may be complications for weeks, months or years and may after the initial infection. The most common is recurrent arthritis, which affects large joints such as the knees causing severe pain and swelling, leading up to disability. Arthritis occurs in up to 60 percent of patients (Steere, 2005). There may be other manifestations of the nervous system such as cerebellar ataxia, myelitis and encephalitis. If the Lyme disease spirochete affect the meninges of the brain caused meningitis. If there is an infection and consequently inflammation of nerves in the brain occurs primarily paralysis of one side of the face. Moreover, disorders of the heart, may appear such as chest pain, dyspnea on exertion,

paplitations, arrhythmias and syncope. Less common is the myopericarditis and heart failure (Halperin, 2014).

Diagnosis

The diagnosis is based on clinical picture as well as on laboratory tests. The clinical diagnosis of Lyme disease can be simple in patients with a history of exposure to ticks and the typical finding of erythema migrans (CDC, growing red spot or papule with a size of at least 5 cm with or without central clearing). The fast and long extension of lupus lesion is diagnostic for ME, whereas before the blockade full examination of the skin must be realized (Wormser et al, 2004). Regarding laboratory tests, according to the CDC batch analysis can be used and if IgG antibodies against *Borrelia burgdorferi* are found there, verification test Immunoblot or Western Blot will be held, because this on its own does not necessarily mean that the patient suffers from borreliosis (Coulter et al, 2007: Nowakowski et al, 2009). Alternatively, the test used polymerase chain reaction (PCR) which has the highest sensitivity for Lyme disease from a sample of synovial fluid of patients (William et al, 2012: Wormser et al, 2007: CDC, 1995).

When symptoms are there for a short time only, the antibodies can not be detected. Besides the detection of antibodies against the bacterium *Borrelia burgdorferi*, indication of meningitis also contributes significantly to diagnosis of Lyme disease. When cultivation is not provided, samples of biopsy are used from the skin wound in patients who have only one migratory erythema, and from plasma in patients with multiple erythema migrans (Coulter et al, 2007: Nowakowski et al, 2009).

Treatment

Early diagnosis and appropriate antibiotic treatment of Lyme disease is important for the prevention of complications and chronicity. Many patients in the early stage can be effectively treated with oral antibiotics to eradicate the microbe. These include doxycycline, cefuroxime or amoxicillin in the absence of neurological manifestations. Doxycycline is not recommended during pregnancy or lactation and in children younger than 8 years

(Girschick et al, 2009). Patients with certain neurological or cardiac forms of the illness may require intravenous treatment with drugs such as ceftriaxone or penicillin. Ceftriaxone also is effective for the treatment of early-stage disease in the absence of neurological symptoms, not used because of serious side effects. In patients allergic to penicillin may be given erythromycin or cefuroxime (Wormser et al, 2006). Moreover due to the increased probability for the occurrence of disturbances, the following are not recommended for the treatment of patients with any manifestation of disease Lyme: first generation cephalosporins, fluoroquinolones, carbapenems, vancomycin, metronidazole, tinidazole, amantadine, ketolides, isoniazid, trimethoprim-sulfamethoxazole, fluconazole, benzathine penicillin G, combinations of antimicrobials, long term antibiotic therapy, hyperbaric oxygen, ozone, intravenous immunoglobulin, cholestyramine, intravenous hydrogen peroxide (Luger et al, 1995). According to many studies, the antibiotic treatment of Lyme disease is effective because most patients recover within a few weeks. Many experts recommend doxycycline as the preferred antibiotic because of its activity against other tick-borne diseases, for example, human granulocytic anaplasmosis, which can occur in up to 10 percent of patients with disease of Lyme (Wormser et al, 2007). Extended treatment with doxycycline from 10 to 20 days, or adding an additional dose of ceftriaxone in principle not improve the therapeutic efficacy in patients with erythema migrans (Nowakowski et al, 2009). An advanced stage of Lyme disease can be effectively prevented with antibiotic therapy (CDC, 1995). Approximately 10-20% of patients (particularly those who are diagnosed later) after antibiotic therapy, may have persistent or recurrent signs and symptoms such as fatigue, musculoskeletal pain, concentration problems or short term memory with or without clinical or laboratory evidence (Girschick et al, 2009). In pediatric patients responding to first-line treatment was comparable to that of adults (Wormser et al, 2003). In an endemic area a retrospective study was conducted from January 1, 2000 to December 31, 2004 to monitor people who

have been diagnosed with early disease Lyme. In this study, therefore, found that patients treated for 10 days with antibiotic therapy have long-term effects similar to those of patients treated longer. Also treatment failure after appropriate, targeted therapy short course, is extremely rare (Girschick et al, 2009; Coulter et al, 2007). When the ME cannot be reliably distinguished from outpatient bacterial cellulitis, a reasonable approach is to treat with either cefuroxime or amoxicillin-clavulanic acid (dosage of amoxicillin-clavulanic acid for adults, 500 mg 3 times a day for children, 50 mg / kg per day in 3 divided doses [maximum of 500 mg per dose]) because these antimicrobials are generally effective against both types of infection (Wormser et al, 2007). The appropriate choice of antibiotic treatment as shown in Table 1, depends primarily on the stage and symptoms of the disease. When the disease spread to other organs, the effectiveness of treatment is limited. For the relief of symptoms of joints may be used NSAIDs. Placing a stent can help the affected joint discharged. If the afflicted knee joint, the patient may use crutches to avoid charging by weight (Wormser et al, 2007). According to recent data has been shown that the application of acaricide to deer tails prevents ticks as hosts to use them and thus reduce the risk for disease Lyme. Also, the application of pesticides in endemic areas helps to reduce the population of ticks. However, it may be harmful to other wild animals but for the people themselves (Oxford Journals, 2011).

Nursing Intervention

Nursing care focuses primarily on prevention of Lyme disease in order to prevent disease recurrence and chronicity of this, but also treat the symptoms when someone is ill and hospitalized. The nurses must know the exact mode of administration of the medication in these individuals, but also to continuously monitor the level of their situation in order to identify any improvement or deterioration. In case of worsening symptoms should design and implement the necessary interventions. It is also vital to provide adequate and accurate information about the disease by health professionals. To the fact that there is no

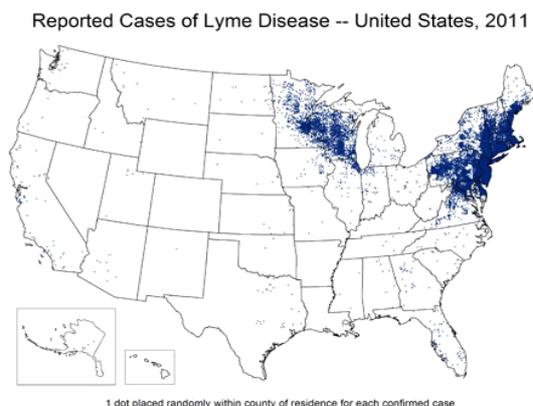
vaccine and that many people do not take any precautions against operators leads measures necessary and important.

Table 1. Antibiotic therapy for early burgdorferi infection

Early manifestations (days to a few weeks after the tick bite)		
Defect area	Symptoms	Antibiotic therapy
General symptoms	"Influenza- like disease"	• Amoxicillin 50 mg/kg/day in three divided doses (maximum dose 1,500 mg/day)
		• Doxycycline 4 mg/kg/day in two divided doses (maximum 200 mg/day, after 8 years of age) for 14 days
Skin	Erythema migrans	• Amoxicillin 50 mg/kg/day in three divided doses (maximum dose 1,500 mg/day)
		• Cefuroxime axetil 20 to 30 mg/kg/day in two divided doses (maximum 1,000 mg/day) for 14 days or 28 days
Neurological disease	Lymphocytoma	for 28 days
	Lymphocytic meningitis	• Intravenous (IV) Ceftriaxone 50 mg/kg/day in one dose (maximum dose 2,000 mg/day)
Cardiac disease	Cranial neuritis, in particular facial nerve	• IV Cefotaxime 200 mg/kg/day in three divided doses (maximum dose 6,000 mg/day)
	Myopericarditis	• IV Penicillin G 0.5 million U/day in four to six divided doses (maximum 20 million U/day) for 14 days
Eyes	Conjunctivitis (in case of influenza- like disease)	• Doxycycline 4 mg/kg/day in two divided doses (maximum 200 mg/day, after 8 years of age) for 14 to 28 days
		• Amoxicillin 50 mg/kg/day in three divides doses (maximum dose 1,500 mg/day)
Joints, muscles	Arthralgia	• Doxycycline 4 mg/kg/day in two divided doses (maximum dose 200 mg/day, after 8 years of age) for 14 days

Source: (Hermann J Girschick. Henner Morbach & Dennis Tappe)

Figure 1. Areas of outbreak of Lyme disease in the USA



Source: (National Center for Emerging and Zoonotic Infectious Diseases)
<http://www.cdc.gov/lyme/stats/maps/interactiveMaps.html>

Taking all the above facts into account it is understood the importance of taking a detailed history if patient remains hospitalized with prolonged symptoms that converge with the clinical manifestations of the disease. Also, given that these patients receiving prolonged antibiotic therapy require extensive monitoring for complications and the risk of allergic reactions from this. Finally we shouldn't forget the personalized education of the individual and the environment, and psychological support if necessary.

Some simple protection measures than can be taken and be suggested are the following:

- Areas where ticks are endemic, such as forests and bushy areas with high grass and leaf waste, must be avoided especially in the warmer months (April to September).
- Wear clothing with long sleeves and pants, and tall rubber boots, so there is no exposed skin.
- Before one out in the countryside, it is important to be sprayed with repellent containing 20 to 30% DEET (N, N -diethyl-m - toluamide) to exposed skin and clothing, which lasts up to several hours.

- To use products containing permethrin spraying clothing and gear. Also there are pre-treated clothing available for extra protection.

- During return must be controlled throughout the skin for the presence of ticks, as well as pet and tools. Parents should monitor their children under the arms, in and around the ears, inside the belly button, behind the knees, between his legs around his waist, and especially in their hair.

- Attached ticks were removed with fine forceps. The tick should be apprehended as close to the skin surface can be removed and a constant pressure. If the head of the tick remains attached to the skin, it can cause as parasitic bacteria in the gut (McPhee et al, 2008).

Conclusions

Lyme disease is a disease that although it does not display much impact in countries of Europe, it is endemic in many parts of America. A significant proportion of people suffering from this disease will show symptoms even after the end of treatment without the cause of this development to be unambiguous. There is a significant lack of knowledge regarding to the natural course of

the disease and also a limited number of studies as far as the effectiveness of antibiotics and the strategies of treatment are concerned in the international literature. Further research on diagnostic methods that can be used is vital and on the appropriate treatment after the disease is diagnosed. The fact that there is no vaccine available for the disease makes the contribution of nurses, doctors and the community as well, in preventive methods to reduce risk factors for infection of the Lyme disease.

The continuous training and updating of health professionals constitutes a particular challenge for health systems with their main purpose being a holistic approach to patients and thereby the provision of better healthcare services. Health professionals should possess the necessary knowledge and skills regarding the prevention and treatment of infectious diseases, such as the Lyme disease, participating in seminars and special workshops promoting thereby lifelong learning.

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