

Lyme Disease

What is Lyme disease?

Lyme disease is an infectious and inflammatory illness caused by a bacterium, *Borrelia burgdorferi*, which is transmitted to animals and human beings through the bite of infected ticks. An alternative name is *borreliosis*. Lyme disease was first described in the USA in the town of Old Lyme, Connecticut in 1975. Increased research efforts resulted in the identification of *B. burgdorferi* as the causative agent in 1981. Today, Lyme *borreliosis* is focally endemic. Cases originate throughout temperate regions of North America, Europe and Asia. *B. burgdorferi* is maintained in regular cycles between ixoid ticks (*Ixodes ricinus* in Europe, and *Ixodes scapularis* and *Ixodes pacificus* in the USA) and small mammal populations.

Genetic variation in *B. burgdorferi* isolates from different geographic regions may explain observed differences in the clinical manifestations of the disease in Europe and North America. Arthritis is more common in the USA. In parts of Europe, chronic dermatologic manifestations and some neurological manifestations are associated with different strains. Lyme disease is probably the most common tick-borne bacterial disease in the world. The disease is not considered to be contagious between people or directly from animals to man. Infection rates in tick populations vary by species and geographical distribution from as few as two per cent to 90 per cent or more. Transmission by biting insects such as flies, fleas or mosquitoes is speculated but appears to be quite rare.

In about 50 per cent of the cases, a characteristic rash or lesion called *erythema migrans* is seen; in Greek, "erythema" is an expression for reddish skin, while "migrare" is a Latin verb meaning to move or to hike. The rash begins a few days to a few weeks after the bite of an infected tick and generally looks like an expanding red ring. The skin reaction can be confused with poison ivy, spider or insect bite, or ringworm.

Blood testing for Lyme disease identifies antibodies that are specific to resisting *B. burgdorferi*. A positive test can be diagnostic when appropriate symptoms are present. However, it is possible to have a negative test during the course of the disease or following antibiotic therapy and still have Lyme disease. At about the same time that the rash develops, influenza-like symptoms may appear with headache, stiff neck, elevated body temperature, muscle aches, fatigue and general malaise. Some people develop the influenza-like symptoms without getting a rash.

If ignored, the first stage of Lyme disease may fade away, but more serious symptoms can develop months or years later. These include muscle and joint pain, usually of the large joints and neurological symptoms such as meningitis, numbness,

Lyme disease is caused by a bacterium transmitted by tick bites. It can affect many organs of the body. Scientific progress has resulted in several antibiotics. Further research promises new tests, medicines and vaccines.





Electron-microscopic picture of *Borrelia burgdorferi*

and burning sensations in the extremities, severe pain, fatigue and depression. Other organs of the body may become involved and heart, eye (Bell's sign), respiratory and gastrointestinal problems can develop. Symptoms are often intermittent lasting from a few days to several months and sometimes years. Because of its diverse symptoms, late stage or chronic Lyme disease, mimics many other illnesses and can be difficult to diagnose. Once a person has recovered from the disease it appears to be possible to be reinfected. Although some deaths have been attributed to Lyme disease, it is not generally considered to be fatal.

Who does Lyme disease affect?

Incidence by age has two peaks. One peak occurs at five to nine years and another at 50 to 54 years. The incidence in children aged five to nine years is approximately twice as high as that in adults. In Europe most cases occur in Scandinavia and Central Europe. As in the United States, there are areas of endemicity in which the annual incidence reaches 160 per 100,000 inhabitants.

European incidence rates are similar to those in the USA. Some 70 cases per 100,000 people were reported in endemic areas such as southern Sweden, with peaks at ages five to nine years and 60-69 years. Reports from Europe also indicate that among children, the rate is slightly higher in boys than in girls, but, in the older age peak, more women were reported than men. Incidence is lowest in individuals aged 20-24 years. There are more than 16,000 cases of Lyme disease per year in the USA.

Present treatments

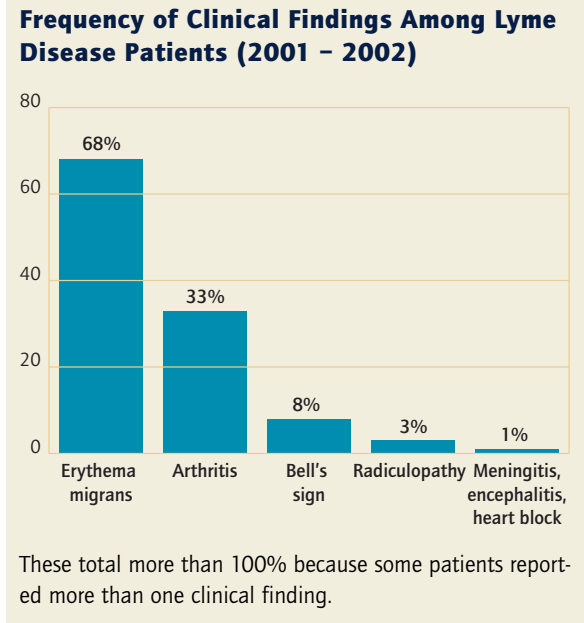
Lyme disease is treated with antibiotics, which are prescribed based on disease stages and manifestations. Compounds of the class of tetracyclines, macrolides, cephalosporins and derivatives of penicillin are some of the choices. Anti-inflammatory medications, such as non-steroidal anti-inflammatory drugs (NSAIDs), are sometimes prescribed to relieve joint stiffness.

If diagnosed in the early stages, the disease can be cured with antibiotics. Timely treatment increases chances of recovery and may lessen the severity of any later symptoms. Treatment for later stages is more difficult often requiring extended and repeated courses of antibiotic therapy. Treatment failures and relapses have been reported.

What's in the development pipeline?

The major goals of Lyme disease research programmes are to develop better means of diagnosing, treating, and preventing the disease. Recently, medical researchers have developed a new blood test that may dramatically improve the value of the laboratory in diagnosing early cases of Lyme disease. The new technique isolates specific immune complexes, which form early in the disease when protective antibodies bind to proteins on the surface of the bacteria. Current testing methods detect only unbound antibodies, which are often not present in sufficient numbers at the first stage of the disease to provide reliable test results.

Research is also ongoing to determine whether long-term antibiotic treatment results in further improvement among patients who have already received the standard treatment. Scientist are also studying whether the brain abnormalities in Lyme disease are primarily due to blood vessel inflammation or a nerve metabolism problem. Studies are also ongoing to identify clinical or biological markers that might be associated with treatment response.



There have been two *B. burgdorferi* recombinant outer-surface lipoprotein A (OspA) vaccines. These were found to be 70 to 90 per cent effective in preventing Lyme disease after three injections. The duration of the protective immunity generated in response to the vaccines has not been established. One vaccine was commercially available in the USA from 1998 but was withdrawn from the market in 2002. Ongoing pre-clinical studies on the development and testing of other candidate vaccines include decorin-binding protein A (DbpA) as a target. In animal studies, scientists have shown that a vaccine composed of the DbpA and OspA is more effective than either one alone in preventing the development of the disease. On the basis of these encouraging findings, research is ongoing to develop a second-generation vaccine to prevent Lyme disease in humans.



The longer-term future

The development of an effective vaccine against Lyme disease and the improved understanding of its long-term outcome are considered to be the most important challenges in the field of future research.

The sequencing of the *B. burgdorferi* genome has opened the door for an increased understanding of the biology of the causative agent and its rapid adaptation to different hosts and environments.

Explaining the pathophysiology of chronic borreliosis of the central nervous system and treatment-resistant Lyme disease related arthritis are a prerequisite for the eventual development of effective treatments for these conditions. In the late stage of the disease, *B. burgdorferi* induces an immune response leading to symptoms in various organs, with little evidence of bacterial invasion. Studies of Lyme arthritis have shown that the chronic inflammatory reaction in the joints is associated with the formation of immune complexes and the production of pro-inflammatory cytokines. Also the involvement of genetic factors, such as human leukocyte antigen (HLA)-DR4 and HLA-DR2, has been shown. These seem to be promising targets for a better treatment of the late stage of the disease.

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