



Lyme Borreliosis

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Lyme borreliosis (Lyme disease) is an infection caused by *Borrelia burgdorferi*, spiral bacteria that are transmitted by bites from infected ticks of the *Ixodes ricinus* complex. It is acquired in temperate regions of the northern hemisphere, usually in forested, woodland or heathland areas, which support the life-cycles of ticks and the small mammals and birds that are reservoir hosts for the bacteria.[1,2] Several pathogenic genospecies of *B. burgdorferi* have been identified, and there is evidence for some variation in types of clinical presentations caused by the different genospecies.

The most common manifestation of Lyme borreliosis is a slowly expanding rash called erythema migrans, which spreads out from a tick bite, usually after about five to fourteen days (range from three to thirty days). It is not usually significantly painful or itchy and may gradually enlarge over many weeks if not treated with antibiotics, but will eventually disappear without treatment. In some cases the leading edge of the rash may become more deeply demarcated, and the central area can return to a more normal appearance, thus causing a ring-like or bull's-eye pattern. Some rashes are very pale and can easily be missed. They may become more noticeable after exercise or a bath, when the skin is generally more flushed. Other symptoms, including tiredness, headaches, aches and pains in muscles and joints may also be present.[1,2]

If the infection is untreated it may spread in the bloodstream and lymphatics to other parts of the body, including the nervous system, joints and other organs, and some patients may develop complications caused by tissue damage. None of the features of the later stages of Lyme borreliosis is unique to the infection, but may also occur in many other conditions.

In the UK the most common complications are associated with the nervous system. These include facial palsy, lymphocytic, 'viral-type' meningitis, meningoencephalitis and radiculopathy (nerve inflammation), which can cause pain, altered sensation or weakness of a limb.[1,2,3] The pain associated with radiculopathy may be similar to that experienced in shingles. These complications usually occur after a few weeks of infection, although radiculopathy may only be recognised after several months. American studies have shown that nervous system complications can occur in 10-15% of previously untreated patients, but even if their condition is not diagnosed and they remain untreated, the symptoms usually resolve or improve within months.[1] Prompt treatment helps to resolve symptoms much more rapidly, and patients with severe painful radiculopathy usually have markedly reduced symptoms and analgesia requirements within a short time of starting antibiotics. Meningoencephalitis is an uncommon complication. It responds to antibiotic treatment, but recovery can take some time and may be incomplete in some patients, depending on the level of tissue damage that had been sustained. Early treatment helps to minimise the risk of complications.

A small number of previously untreated patients may progress to late neuroborreliosis, with brain and spinal cord tissue damage, so it is important that treatment is given at an early stage to minimise risk of progression to this unusual but potentially serious complication. It has been estimated that late Lyme encephalomyelitis occurs in no more than 1 in 1,000 cases of untreated Lyme borreliosis.[3] Fewer cases have been reported in recent years, due to greater awareness of Lyme borreliosis leading to earlier diagnosis and treatment.

Lyme borreliosis can also trigger inflammation of large joints, usually the knee. This is a rare complication of infection acquired in the UK, but is more frequently seen in patients who became infected in North America or some parts of mainland Europe. Most patients respond well to antibiotic treatment, but a minority may develop persistent

supporting people in the UK, the Republic of Ireland and worldwide

arthritis, which can occur when a patient's immune system responds to *Borrelia burgdorferi* also attack his or her own joint tissues. Some people have a genetic predisposition to developing this complication, which has been termed antibiotic-refractory arthritis.[1] Multiple or prolonged courses of antibiotics are not helpful, but anti-inflammatory drugs which are also used in other types of arthritis may be valuable for symptomatic relief while the condition resolves over time.

The skin condition acrodermatitis chronica atrophicans (ACA) is a late complication of untreated European-acquired Lyme disease, especially in Scandinavia. Some cases have occurred in the UK. Affected skin becomes atrophic and there may be some accompanying sensory loss.[2] The condition is caused by longstanding active infection and will respond to antibiotic treatment, but very severe atrophic changes may not completely resolve, because of the degree of tissue damage.

Other uncommon complications of Lyme borreliosis include heart involvement, mainly conduction defects leading to slowing or irregularity of the heart beat rhythm. This usually occurs within a few weeks of infection and usually resolves completely. It is rare in the UK. Very few cases of chronic cardiomyopathy have been described in the world literature. Uveitis, tendonitis and myositis have also been reported.[1,2]

Historical note

Lyme borreliosis, and its association with tick bites, was recognised in the USA in the mid-1970s, initially as Lyme arthritis, when a cluster of juvenile arthritis cases was investigated in Lyme, Connecticut. European workers had described many of its skin and neurological manifestations in articles dating back to the nineteenth century, and recognised the association with ticks. Erythema migrans was first described by Afzelius, a Swedish clinician, in 1910, ACA by Buchwald in Germany in 1883 and Nikulin, a Russian physician, in 1896. Neurological manifestations were described by Garin and Bujadoux in France in 1922, Hellerstrom in Sweden in 1930 and by Bannwarth in Germany in 1941. Antibiotics were used empirically to treat some patients from 1949, although the bacterial cause was proven by American workers only in 1981.

Diagnosis and laboratory tests

Lyme borreliosis occurs only in people who have been bitten by infected ticks. It is important that a patient's risk of exposure to ticks is properly assessed and the clinical history evaluated for features compatible with Lyme borreliosis before requesting diagnostic tests.[4] It is more useful to assess a patient's tick exposure risk than simply ask about tick bites, as many tick bites go unnoticed. Tests should not be used for 'screening' if there is little clinical and epidemiological likelihood that the patient has the infection, as the predictive value of a positive result in this situation is very low. False-positive tests may lead to misdiagnosis and inappropriate and possibly dangerous treatment.[4,5,6]

The usual tests look for the presence of antibodies to *Borrelia burgdorferi*, i.e. the patient's immune system response to the infection, rather than detecting the organism itself. The reliability of *B. burgdorferi* antibody tests is similar to that for many other infectious diseases when tests are applied and interpreted appropriately.[7] Antibodies may not be detectable in the first few weeks after infection (30-70% positivity depending on duration of infection), but it is rare for tests to be negative in late stage disease.[4,5] It is not necessary to perform laboratory tests to confirm a confidently-made clinical diagnosis of erythema migrans, but laboratory evidence should be sought to support a diagnosis of later-stage infection, as none of the later presentations is unique to Lyme borreliosis. More complex investigations may be helpful if later-stage Lyme borreliosis is still suspected despite negative antibody tests. Antibody tests on CSF can also be useful in suspected neuroborreliosis.

A two-stage antibody test procedure is currently recommended by both European and American experts to minimise the risk of false-positivity. The first stage uses a sensitive screening method. False-positive results can occur in first stage tests on samples from patients with many other

conditions, including glandular fever, rheumatoid arthritis or syphilis. More detailed and specific immunoblot (western blot) tests should be performed on all specimens reacting in preliminary tests, to establish whether these reactions are true-positive or false-positive. These second-stage tests require special expertise to perform and interpret, and are available in specialist laboratories.

The clinical significance of results should be assessed carefully in the light of the patient's clinical and tick exposure history [1,2,4,5] Patients may have positive tests for *Borrelia burgdorferi* antibodies for an indefinite period after appropriate treatment.[1,2,4,5] This does not indicate that the treatment has failed; success or failure should be judged primarily on clinical findings. Other specialised investigations may be helpful if a clinician is concerned that a patient may have had an inadequate response to treatment. Some patients, especially those whose work or residence exposes them to risk of frequent tick bites, may be seropositive because of past infection, which may have been asymptomatic or unrecognised.[1,2] Their current clinical problem may be unrelated to their previous infection, again emphasising the importance of clinical assessment and evaluating laboratory findings in the overall context of a patient's illness.

Direct methods to detect *B. burgdorferi* include culture and borrelial DNA detection techniques. These are mainly used in research. Culture requires special growth media and may take three to six weeks. It has a 50-80% yield from skin biopsies of erythema migrans, but is rarely successful from urine, CSF or joint fluid and is not routinely available.[1,4] Borrelial DNA detection by polymerase chain reaction (PCR) is helpful in certain clinical situations, especially for synovial fluid in with suspected Lyme arthritis. It is also useful for skin biopsies, but has limited value for CSF and is not recommended for blood and urine samples.[4,5]

Some tests available in certain commercial laboratories have been proven in independent studies not to be of value. One is the Lyme urinary antigen test (LUAT), which purports to detect borrelial antigen in urine. [8] Claims have also been made for the QRIBb and FACS tests, rapid methods using fluorescent microscopy to identify borreliae in blood and other fluids. All are grossly inaccurate.[9] Other unreliable tests include the lymphocyte transformation test (LTT) and unorthodox applications and interpretations of immunoblots. Direct microscopy of blood is also inappropriate and has no scientific merit.

Treatment

The treatment guideline published by the infectious Diseases Society of America in 2006 is authoritative and comprehensive.[10] The American Academy of Neurology published excellent guidelines for neuroborreliosis treatment in 2007.[16] Both are similar to the recommendations of various European expert groups.[2] The oral antibiotics doxycycline (adult dose 100mg bd), amoxicillin (adult dose 500mg tid) or cefuroxime axetil (adult dose 500mg bd) are recommended for two weeks for treating erythema migrans and isolated facial palsy and for four weeks when treating patients with Lyme arthritis. Intravenous treatment with ceftriaxone (adult dose 2g daily) for two weeks is recommended for other neurological presentations. Oral doxycycline (adult dose 100-200mg bd) is also recommended in some cases of acute neuroborreliosis. Clinical features of late neuroborreliosis may be slow to resolve, as damaged nerve tissue is slow to heal. Re-treatment may be indicated in occasional cases of arthritis and neuroborreliosis, but there is no evidence that prolonged or multiple courses of antibiotics are valuable,[1,2,10] and they can cause serious and even fatal adverse effects.[6] Erythromycin is not recommended for treating any stage of Lyme borreliosis, as it has a high failure rate. Newer macrolides such as azithromycin or clarithromycin may be used if first- and second-line antibiotics are contraindicated, but patients should be carefully followed up as treatment failures may occur.

England and Wales epidemiology (provisional figures for 2007)

During 2007, 797 serologically confirmed cases were reported; age, sex and seasonal distributions were similar to previous years. The male:female ratio was approximately 1:1; 11% were in children aged <15 years and 46% in people aged 45-64 years. Almost 50% of cases were reported in

the third quarter of the year. This represents a likely peak onset of symptoms in early summer, consistent with the major tick feed period in late spring-early summer. Neurological presentations were steady at 67 cases (8.3%).

Most people acquired infection through recreational or residential risks. Only 16 (1.8%) were known to be occupationally acquired, mainly in forestry and farm workers, soldiers, outdoor instructors and deer handlers. The proportion of travel-associated infections was similar to recent years, with over 20% of all reported cases known to have been acquired abroad, mainly by holidaymakers visiting the USA, France, Germany Scandinavia and other European countries. Over 60% of indigenously acquired infections were acquired in southern counties of England, comprising the South-West and South-East Health Regions. A further 11% came from counties in the Eastern Health Region. These areas include well-known foci of Lyme borreliosis around the New Forest, Salisbury Plain, Exmoor and Thetford Forest. Other endemic areas include the Lake District, Yorkshire moors, Scottish Highlands and Islands and many woodland areas in southern England.

Prevention

People acquire Lyme borreliosis through bites from infected ixodid ticks, the vector hosts. The infection cannot be passed person-to person, nor from other animals. Peak times for tick blood meals are late spring, early summer and autumn, although there may be a low level of tick feeding activity in mild winter periods. The main feeding hosts for larval and nymphal ticks are small mammals such as field mice and voles, and birds including blackbirds and pheasants.[2] These hosts may also be reservoirs of *B. burgdorferi*, and the tick feeding patterns ensure the organism's continuing cycle between generations of reservoir and vector hosts. Humans are incidental hosts for tick feeds. Fortunately only a minority of ticks carry borreliae, and borrelial transmission usually occurs late in the feed. It is unlikely to occur in the first 18-24 hours of attachment. A detailed review is provided in reference 10.

Human infection risk can be minimised by:

- Tick-awareness.
- Wearing appropriate clothing in tick-infested areas (long sleeved shirt and long trousers tucked into socks). Light coloured fabrics are useful, as it is easier to see ticks against a light background
- Using insect repellents, e.g. DEET-containing preparations.
- Inspecting skin frequently and removing any attached ticks.
- Checking again for ticks, especially in skin folds, at the end of the day.
- Making sure that children's head and neck areas, including scalps, are properly checked.
- Checking that unfed ticks are not brought home on clothes.
- Checking that pets do not bring unfed ticks into the home on their fur.

Remove ticks by gently gripping them as close to the skin as possible, preferably using fine-toothed tweezers or similar implements, and pulling steadily away from the skin.[12] Some veterinary surgeries and pet supplies shops sell inexpensive tick removal devices, which are useful for people frequently exposed to ticks. Lighted cigarette ends or match heads should not be used. Some experts consider that using volatile oils or other substances to cover a tick and force it to detach may increase risk of borrelial transmission, as they could stimulate the tick to regurgitate potentially infected material.

Antibiotic prophylaxis following a tick bite is not currently routinely recommended. (See reference 10 for further discussion.) No vaccine is currently available in Europe or the USA.

Co-infections

Other infections can be transmitted by bites from infected ticks, including anaplasmosis and babesiosis. Both are rare diseases in the UK, but babesiosis may cause overwhelming infection in individuals who have had their spleens removed. A patient with Lyme borreliosis may have atypical clinical features if a co-infection is also present. Clinicians should be aware of the possibility of co-infections, which may also influence treatment choice. (See reference 10 for more detailed discussion.)

Controversies in Lyme borreliosis

Seronegative Lyme borreliosis

Antibody tests are likely to be negative in the first few weeks of infection, but it is rare for patients with late stage Lyme borreliosis to be seronegative. None of the features of later stage Lyme borreliosis is unique to the infection, and the patient's history should be carefully re-evaluated for other diagnostic possibilities before a diagnosis of seronegative Lyme borreliosis is accepted.[2,7,17] Additional specialised antibody and PCR tests to look for evidence of *B. burgdorferi* infection can be helpful.

Post Lyme syndrome

A few patients may continue to have subjective symptoms after appropriate treatment, similar to chronic fatigue syndrome or fibromyalgia.[1,2,10,17] They should be carefully re-evaluated, including a review of their previous treatment and should be re-treated if there is objective evidence of active infection or if their previous treatment was inappropriate. Prolonged or multiple courses of antibiotics are not indicated. Many other conditions, infectious and non-infectious, may also trigger similar symptoms.[10,17] A large American study showed that the frequency of pain and fatigue was no greater in patients who had had Lyme disease than in age-matched controls who had not had *B. burgdorferi* infection.[1] Another study showed that patients with post-Lyme syndrome who were re-treated with prolonged courses of antibiotics had similar outcomes to those who received placebo for the same duration.[11] Such patients are best treated symptomatically rather than with prolonged antibiotics, which can cause life-threatening complications.[10,17]

Information on the Internet

Some websites give excellent information about Lyme borreliosis, but others are grossly inaccurate, promoting potentially harmful unorthodox approaches to diagnosis and treatments. (13,14,15) The International Lyme and Associated Diseases Society (ILADS), a fringe medical group, promulgates inaccurate information on the diagnosis and management of Lyme disease. [13,15]

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Useful websites:

Health Protection Agency <http://www.hpa.org.uk>

EUCALB (European Concerted Action of Lyme Borreliosis) <http://www.oeghmp.at/eucalb>

American College of Physicians <http://www.acponline.org/> (enter 'Lyme' in search field):

Centers for Disease Control (CDC) <http://www.cdc.gov/ncidod/dvbid/lyme/index.htm>

<http://www.cdc.gov/ncidod/dvbid/lyme/bibliography.htm> (scientific references)

http://www.cdc.gov/ncidod/dvbid/lyme/resources/LD_Internet.pdf (scientific references)

American Lyme Disease Foundation (ALDF) <http://www.aldf.com>

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