

# Lyme Disease

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Lyme disease (Lyme borreliosis) is caused by the tick-borne spirochaete *Borrelia burgdorferi*. Erythema migrans, an early skin lesion, is the most common clinical presentation. The organism may spread, causing various later manifestations.

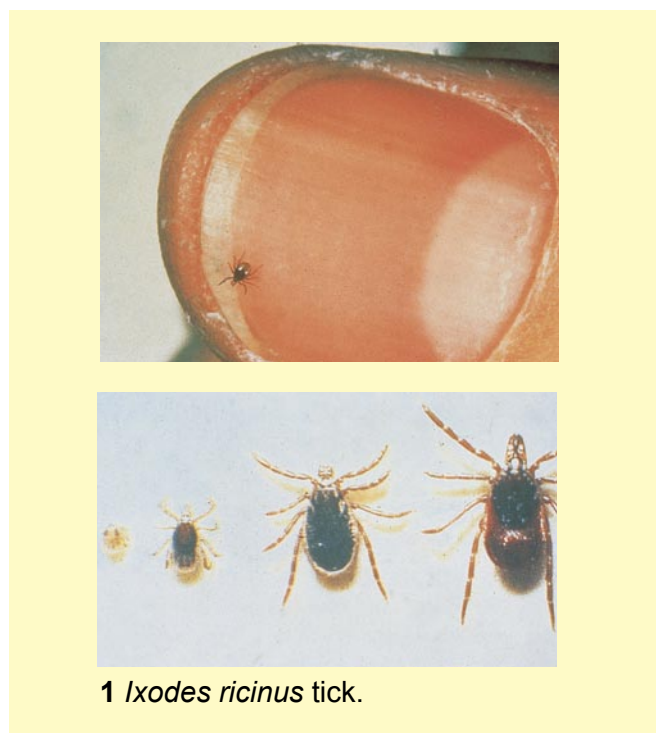
## Epidemiology and environmental factors

Lyme disease is the most common tick-borne infection in the temperate northern hemisphere. More than 10,000 cases were reported in the USA in 1998, predominantly from northeast, Midwest and Pacific coast states. The infection is particularly prevalent in parts of southern Scandinavia, Germany, Austria and other Central European countries. About 500 cases may occur annually in the UK. Infection can occur in any age group, and is most likely in individuals whose residence, or occupational or recreational activities place them at high risk of tick bites.

Ixodid ticks (Figure 1) are the vectors of *B. burgdorferi*. They are common in woodland, heath and moorland, but can also live in semirural areas bordering large population centres. They take a blood meal in each of the three stages of their life cycle, attaching themselves to their hosts by barbed mouthparts. An infected tick may transmit borreliae towards the end of its feed, regurgitating infected saliva into the animal's skin. Reservoir hosts for the spirochaetes include small and medium-sized mammals (e.g. field mice, hares), and birds including blackbirds, pheasants and gulls. Humans are incidental hosts for ticks, and infections occur mainly in late spring, early summer or autumn – the peak periods for tick feeds. The annual incidence of Lyme borreliosis can vary, depending on climatic factors affecting tick population density and activity.

Nymphal ticks are the main source of human borrelial infection, but are very small and may be overlooked. Tick bites may not be recognized because they do not usually cause significant pain, irritation or itch. Individuals who may be exposed to ticks can minimize their risk of infection by wearing protective clothing (light-coloured long-sleeved shirts and long trousers), by checking their skin regularly, and by gently removing any attached ticks. Borrelial infection is unlikely to occur if ticks have been feeding for less than 24–36 hours.

Ixodid ticks may also carry other organisms including ehrlichiae, babesiae and Central European tickborne encephalitis virus. Co-infections have been documented and may cause atypical presentations.



## Pathogenesis

*B. burgdorferi* can spread via the bloodstream and lymphatics to many tissues, and may migrate through the blood–brain barrier, evading the host’s immune responses. It alters its outer surface protein (Osp) expression, from OspC in the early stage to others (including OspA and OspB) in established infection, which may help it evade host response. Lyme arthritis may manifest partially by cytokine activity, and some studies have suggested that certain individuals (particularly those who are HLA-DR4 positive) may be genetically predisposed to chronic Lyme arthritis. Autoimmune factors have also been implicated in the pathogenesis of neuroborreliosis, in addition to direct spirochaetal invasion and mediation by cytokines. Antibodies produced in response to spirochaetal antigens may cross-react with axonal tissue components.

At least three genospecies of *B. burgdorferi* are pathogenic, and borrelial heterogeneity is significant in organotropism and disease presentation. Only one genospecies (*B. burgdorferi sensu stricto*) appears to cause human infection in North America. At least two other pathogenic genospecies are also found in Europe – *B. garinii*, which is particularly associated with neurological complications, and *B. afzelii*, which is associated with later skin manifestations. Antigenic heterogeneity has implications for vaccine strategies.

## Clinical features

Infection can be asymptomatic, but clinically significant disease may be divided into three stages. Progression to later stages is not inevitable, even in untreated patients.

**Localized (stage I) borreliosis** – the most common and often only clinical manifestation of Lyme disease is erythema migrans, a localized erythematous rash appearing 2–30 days (usually 7–15 days) after a bite (Figure 2). The rash may be faint, with a more pronounced margin that gradually migrates outwards to produce a sizeable lesion. A central area of clearing may become evident as previously affected skin returns to normal. There may be local lymphadenopathy.

**Early disseminated (stage II) borreliosis** – in the following months, the organism can affect many tissues, principally the nervous, musculoskeletal and cardiovascular systems and the skin. There may be a flu-like illness with myalgia and arthralgia. Multiple areas of erythema migrans can occur, but are uncommon in infections acquired in the UK. Early neurological presentations include isolated facial palsy, which may be bilateral, other cranial nerve lesions, lymphocytic meningitis and painful radiculoneuritis. Musculoskeletal complications include persistent arthralgia and small joint arthritis. Recurrent episodes of large joint inflammation (usually affecting the knee) may become chronic, despite antibiotic treatment. Cardiac conduction abnormalities (usually mild) are uncommon and cardiomyopathy is rare. Ocular, hepatic and other manifestations have also been reported.

**Chronic (stage III) borreliosis** is uncommon.

- Chronic Lyme arthritis is the most common manifestation in the USA. In a few patients, inflammation may continue for months or even several years after antibiotic treatment, and this may be related to molecular mimicry between borrelial OspA protein and human lymphocyte function-associated antigen, triggering a continuing T cell response in genetically susceptible individuals. There is usually a strong antibody response to *B. burgdorferi*, which can be detected in serum.
- Chronic neurological manifestations include radiculoneuropathy, presenting mainly with sensory symptoms. Lyme encephalopathy is uncommon. Patients may complain of



**2** A 2-year-old girl with erythema migrans. She had been bitten by a tick 15 days previously.

poor memory and concentration, and have subtle learning difficulties. There are usually abnormalities on CSF examination, including raised protein levels and intrathecal synthesis of *B. burgdorferi* antibody. Lyme encephalomyelitis is a rare condition characterized by spastic paraparesis, cognitive impairment, cranial neuropathy, bladder dysfunction and dysarthria. CSF pleiocytosis and intrathecal antibody production occur.

- Acrodermatitis chronica atrophicans is a chronic skin manifestation first described in 1882. Lesions on the limbs are initially violaceous and may last for years, eventually becoming atrophic (Figure 3). They are strongly associated with *B. afzelii* infection, which has been cultured from lesions years after onset, despite a strong antibody response. The condition is often accompanied by peripheral neuropathy.

### Investigations

Diagnosis is largely clinical, particularly in early infection. In non-endemic areas, there may be a low awareness of Lyme disease and the possibility may be overlooked, particularly when the patient experienced only transient or unrecognized exposure to ticks (e.g. on holiday or a day trip).

**Borrelial culture** is slow and has a low yield, even in untreated patients. Borrelial DNA detection by polymerase chain reaction analysis is probably slightly more sensitive in biopsies from suspected erythema migrans and may be useful in the investigation of suspected neuroborreliosis or Lyme arthritis, but target DNA may be present in only very low copy numbers. The method does not differentiate between living and non-viable organisms. Results should be interpreted with care.

**Antibody tests** remain the mainstay of laboratory diagnosis. Screening tests have had a poor reputation, principally because of false-positive reactions in the presence of conditions such as infectious mononucleosis, rheumatoid disease, autoimmune diseases and other spirochaetal infections, leading to incorrect diagnosis and presumed treatment failure. Many US and European authorities recommend that initially reactive and equivocal specimens are also evaluated by immunoblot, to assess antibody specificity to a range of borrelial antigens (Figure 4). Positive tests may reflect past exposure rather than currently active infection, and results must be interpreted in light of the clinical situation.

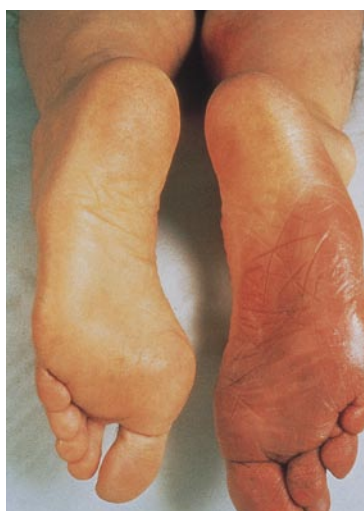
Antibody tests may be negative in erythema migrans, which is primarily a clinical diagnosis made on the typical appearance and history of tick exposure. Prompt treatment may partially or completely ablate the antibody response. Tests are seldom negative in later disease; a diagnosis of seronegative Lyme disease should be made only after careful consideration of alternatives.

### Antibiotic treatment

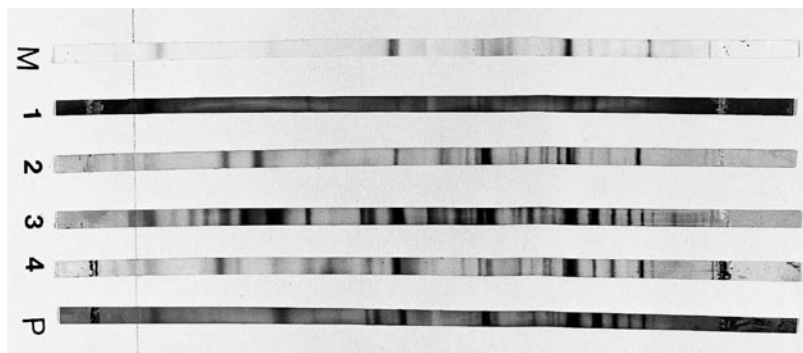
There are two important factors in antibiotic treatment.

- *B. burgdorferi* is slow to replicate, and a longer course is recommended than for 'conventional' bacterial infections.
- *B. burgdorferi* can disseminate widely to tissues which may be poorly penetrated by certain antibiotics.

The most commonly used oral antibiotics are amoxicillin, doxycycline and cefuroxime axetil. Erythromycin and phenoxymethylpenicillin are not recommended because they are unlikely to achieve satisfactory levels in tissue such as CNS and synovium. Azithromycin, though not licensed for this use, could be considered if there are



**3** Acrodermatitis chronica atrophicans.



**4** IgG immunoblot showing specimens from patients with (1) erythema migrans, (2) arthralgia, (3) Lyme arthritis acquired in the USA and (4) Lyme arthritis acquired in Germany.

contraindications to the recommended oral agents. Parenteral antibiotics include benzylpenicillin, ceftriaxone and cefotaxime.

Dose, route of administration and duration vary with the clinical situation; no regimen is clearly superior. A 10–14-day course of oral amoxicillin or doxycycline is recommended in erythema migrans. Disseminated infections may require a 2–4-week course of oral or parenteral antibiotics, but few prospective trials have been performed to assess the efficacy of parenteral antibiotics against oral doxycycline, and the latter should also be considered when ehrlichial co-infection is suspected. Chronic neuroborreliosis should be treated with parenteral agents for 14–28 days.

### Prevention

- Public education programmes are effective in reducing the incidence of infection in endemic areas. Simple, commonsense measures to avoid tick bites and prompt removal of attached ticks can greatly reduce the risk.
- Antibiotic prophylaxis is not routinely recommended after tick bites, but may be considered in special circumstances (e.g. in immunocompromised patients and pregnant women bitten in areas of known high endemicity).
- Vaccines are now available in North America that provide some protection against *B. burgdorferi sensu stricto*, but are unlikely to be valuable in Europe because of genospecies variability. ◆

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### FURTHER READING

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### **Practice points**

- Ticks are tiny and may not be noticed; ask about possible tick exposure rather than a definite history of tick bites
- Absence of a history of erythema migrans does not exclude later-stage Lyme disease – it may have been overlooked or infection could have occurred without a rash
- Antibody tests should not be performed when the pre-test likelihood of Lyme disease is low; positive screening tests should be confirmed by immunoblot
- Antibody tests may be negative in early infection, but patients with late Lyme disease are seldom seronegative

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