

# Lyme disease in the United Kingdom

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## ABSTRACT

Lyme disease, while still an uncommon disease in the UK, is on the increase. Case numbers have increased by 3.6-fold since 2001, with over 950 cases reported by the Health Protection Agency (HPA) in 2011, compared with less than 500 cases annually pre-2004. HPA indications of the true incidence are suggested to be closer to 3000 cases/year, of which around 82% of cases are indigenously acquired. Three genospecies, *Borrelia burgdorferi sensu stricto*, *Borrelia afzelii* and *Borrelia garinii*, represent the predominant pathogenic variants in the UK. Erythema migrans is the commonest manifestation, occurring in 60%–91% of cases. In the UK, neuroborreliosis is the most common complication, while myocarditis is unusual, and death from either conduction disease or carditis is extremely rare. The role of *Borrelia* infection in chronic dilated cardiomyopathy in the UK remains unproven. Controversy over the existence of either ‘chronic Lyme disease’ and/or ‘post-Lyme disease syndrome’ continues unabated. National medical societies, patient advocacy groups, insurance companies, lawyers, doctors, the private health medical sector and scientific journals have all become embroiled in this bitter controversy. New developments include diagnostic tests able to detect Lyme disease at an earlier stage, shorter durations of antibiotic therapy and potential advances in vaccines against *Borrelia*.

## INTRODUCTION

Lyme borreliosis (LB) is the most common vector-borne bacterial infection in the temperate northern hemisphere. Lyme disease is becoming increasingly common in the UK<sup>1</sup> with cases steadily increasing from only 68 cases in 1986 (UK and Irish Republic)<sup>2</sup> to over 950 cases in the UK alone in 2011.<sup>3–4</sup> Lyme disease exhibits multisystem involvement, occurs in stages and may mimic other diseases.<sup>5</sup> It is caused by genospecies of the *Borrelia burgdorferi sensu lato* group. Transmission occurs during the course of blood meals taken by infected hard-bodied ticks of the *Ixodes ricinus* complex. In the UK and Europe, the *I ricinus* tick is responsible, whereas in the USA, the vector is largely *Ixodes scapularis* (on the west coast *Ixodes pacificus* predominates). *Borrelia* spread from the skin to other tissues through both the blood stream and lymphatics. Ticks may infect humans at any point in their life-cycle although it is mainly at the nymphal stage that this occurs. Erythema migrans (EM) is by far the most common clinical presentation occurring in about 90% of symptomatic infections, but neurological, rheumatological, cardiac and other complications also occur.<sup>6</sup>

PCR studies have confirmed the presence of borrelial DNA in European and American ticks stored from the late 19th and early 20th centuries. Tissue from a 5300-year-old neolithic mummy found in

the Italian Alps has also revealed *Borrelia burgdorferi* DNA making ‘Otzi the iceman’ the earliest known human with Lyme disease.<sup>7</sup> While clinical descriptions of LB appear in the literature from 1883, the term ‘Lyme disease’ appeared following a cluster of cases of skin rashes and associated arthritis in children around the town of Lyme in Connecticut.<sup>8</sup> The British public are now regularly exposed to newspaper articles highlighting the features and issues surrounding this disease.<sup>9–10</sup>

Individual *Borrelia* genospecies are not ‘directly’ linked with specific clinical manifestations, although neurological complications are often associated with *B garinii* and *burgdorferi sensu stricto*. Arthritic and cardiac complications most commonly occur with *B burgdorferi sensu stricto* and skin infections with *Borrelia afzelii* mainly cause skin presentations,<sup>11</sup> including an uncommon late manifestation, acrodermatitis chronica atrophicans.<sup>12–13</sup>

We report the current epidemiological data for the UK, describing clinical features and management and provide a review of the ongoing controversies.

## UK EPIDEMIOLOGY

Cases of Lyme disease in the UK have increased by 3.6-fold since 2001 with over 950 cases reported by the Health Protection Agency (HPA) in 2011 (table 1).<sup>3–4</sup>

This equates to a rise in the incidence of serologically confirmed cases from 0.50/100 000 in 2002 to 1.64/100 000 in 2010.<sup>4</sup> However, not all cases are serologically confirmed with the HPA estimating that an additional 1000–2000 cases per year are diagnosed and treated on the basis of clinical features. Of these, up to 800 cases are indigenously acquired, with 18% acquired abroad. Hospital admissions, for Lyme disease in England, are understandably lower than this and have plateaued since 2005 (figure 1).<sup>14</sup>

In the UK, the highest attack rates occur in people aged 45–64 years, followed by those aged 24–44 years, with a roughly equivalent gender distribution.<sup>4</sup> Of indigenous infections, around two-thirds were resident in the southern counties of England.<sup>4</sup> Recognised foci include the New Forest, Thetford, Salisbury Plain, Exmoor, the Lake District, parts of the South Downs, West Sussex, Surrey, Wiltshire, West Berkshire, the Yorkshire moors, the Scottish Highlands and islands and parklands such as the Royal London parks of Richmond and Bushy.<sup>15–16</sup> As a ‘rule of thumb’, deer road signs against a leafy woodland (deciduous) or moorland backdrop can indicate potential Lyme areas.<sup>17–18</sup> Ticks only survive in areas with good vegetation cover and enough decaying vegetation to retain a relative humidity of 80%–85% during dry periods. The mild damp climate of the British Isles is ideally suited to support tick populations.<sup>19</sup>

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**Table 1** Laboratory confirmed cases of Lyme borreliosis for England and Wales, 2001–2011

Year	Total reports
2001	268
2002	340
2003	292
2004	500
2005	595
2006	768
2007	797
2008	813
2009	863
2010	905
2011	959

Infections acquired abroad are usually from endemic regions of France, Germany, Austria, Scandinavia and eastern European areas, such as Slovakia and the Czech Republic and from the USA. Within Europe, the geographic distribution of LB is expanding both towards higher altitudes and latitudes; it now extends from northern Turkey and the Atlas mountains of north Africa to southern Sweden.<sup>18</sup>

HPA indications of a true incidence closer to 3000 cases/year may be partly explained by facilitated migration from eastern and central European countries (regions with high prevalence of Lyme disease) within the European Union to the UK. Increased tourism to these regions is likely to have contributed.

Case numbers in the UK are dwarfed by more than 20 000–30 000 cases/year in the USA,<sup>20 21</sup> and more than 60 000 in Germany.<sup>22</sup> There may be as many as 200 000 cases annually in the whole of Europe. Central European countries, including Austria, the Czech Republic, Germany, Switzerland, Slovenia and Slovakia, have the highest prevalence of Borrelia infected ticks in Europe.<sup>23</sup> The pathogenic genospecies of Borrelia in the UK (*B burgdorferi sensu stricto*, *B afzelli* and *B garinii*) are also largely responsible throughout Europe. In the USA, *B burgdorferi sensu stricto* is almost exclusively responsible for LB.

Human infections will be affected by variations in host populations for ticks (ie, wild deer), climate changes (milder winters) and exposure to regions with infected tick populations. Climatic variation alone (an earlier spring and longer autumn) will influence animal vector populations and hence tick populations, as

well as human host recreational activities (orienteeing, trekking, mountain biking and camping) occupations (farming, game-keeping, forestry, fungi and wild food collecting) and travel in tick endemic areas. About 70% of sero-positive cases identified in the UK are between July and October, corresponding with tick activity in the early summer.<sup>4</sup>

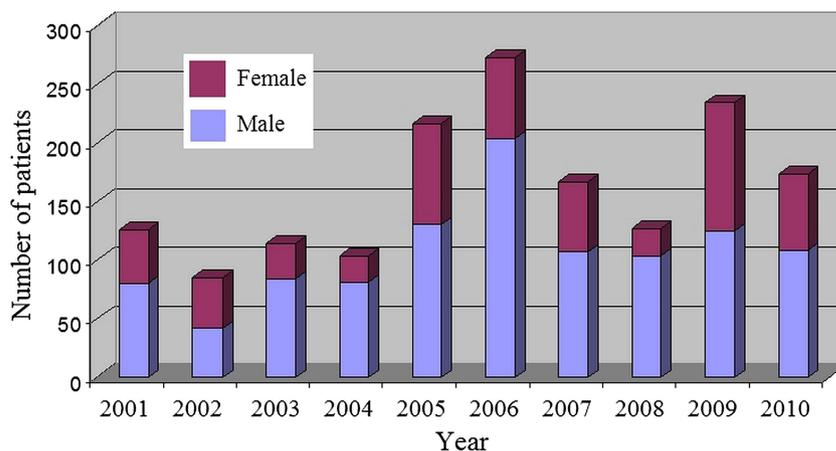
The presence of deer, which are non-competent reservoirs for spirochaetes,<sup>6</sup> is indicative of the factors leading to a 'Lyme-permissive' habitat. While estimates of wild deer populations in the UK are difficult, experts suggest there are more now than at any time in the last 1000 years (around 1.15 million Red and Roe deer and over 300 000 Fallow, Muntjac, Sika and Chinese water deer species).<sup>24</sup> Some estimates suggest the total number of deer may exceed 2 million. Moreover, a German study found an average of 64.5 ticks per Roe deer.<sup>25</sup> More reassuring is the fact that, in the UK, only a minority of ticks carry borreliae. Within Europe, the transmission risk from infected ticks appears low to moderate if attached for less than 24 h.<sup>26</sup> The North American experience suggests a tick will need to feed for at least 36 h before the borrelia bacterium is transmitted from the gut of the tick to the human host.<sup>20 27 28</sup> However, short tick attachment (less than 24 h) should not rule out a diagnosis of Lyme disease.<sup>29</sup>

#### CLINICAL FEATURES OF LYME DISEASE IN THE UK

Lyme disease can result in a wide spectrum of multi-organ involvement and dysfunction. It is frequently self-limiting and resolves spontaneously.<sup>30 31</sup> Death due to Lyme infection is an extremely unusual outcome. In the untreated patient, Lyme disease usually demonstrates three clinical phases (table 2).<sup>20 32 33</sup> This 'staged' pattern of disease is similar to syphilis and leptospirosis, two other infections also caused by spirochaete bacteria.<sup>4</sup>

#### EARLY LOCALISED LB

Early localised borreliosis occurs at a median of 21 days (range 3–82 days) following a tick bite,<sup>16</sup> often with an expanding 'target-like' rash of EM (figure 2). All pathogenic genospecies can cause EM.<sup>18 33</sup> It is the commonest clinical manifestation of Lyme disease in the UK<sup>34</sup> developing in around 60%–90% of cases.<sup>16 35</sup> In a report of 65 cases in the UK, between 2002 and 2007, 91% had EM at presentation.<sup>16</sup> In 2009, a study reported a 74% prevalence for EM.<sup>36</sup> The border can be raised with a diameter of 5–75 cm (mean 15 cm)<sup>20</sup> with a central vesicle or pustule in around 5% of people. However, more subtle forms of the rash may occur in less obvious locations (figure 3).

**Figure 1** Admissions to English National Health Service hospitals with Lyme disease by gender for the years 2001–2010.

**Table 2** Stages and clinical features of Lyme borreliosis

Stages of Lyme disease	Nomenclature	Clinical features
Initial stage	Early localised Lyme borreliosis	Erythema migrans  Flu-like symptoms, limited pyrexia Headache, myalgia, arthralgia, local lymphadenopathy Borrelia lymphocytoma (uncommon and frequently involves earlobe or nipple)
Stage 2	Early disseminated Lyme borreliosis	Multiple erythema migrans lesions (<5 cm diameter and unusual in the UK)  Sweats, myalgia, arthralgia (more severe constitutional symptomatology) Viral-like meningitis and or mild encephalitis VII Cranial nerve palsy (can be bilateral) Other cranial nerve palsies Mononeuritis multiplex Radiculopathies (usually months after the initial infection) Cardiac conduction disturbances Arthritis—recurrent and with joint effusions Myocarditis Pericarditis Cardiomyopathy and heart failure (rare)
Stage 3	Late disseminated Lyme borreliosis	Oligoarthritis (Lyme arthritis)  Acrodermatitis chronica atrophicans

With permission of the *British Journal of Hospital Medicine*.<sup>32</sup> Rare additional manifestations of the early disseminated phase include uveitis, panophthalmitis, hepatitis, myositis and orchitis.<sup>33</sup>

Studies indicate that around 50%–70% of patients recall a tick bite.<sup>20 37</sup> Associated non-specific ‘flu-like’ symptoms include fever, chills, tiredness, headache, arthralgia or myalgia, but a patient may also be asymptomatic in this early phase.



**Figure 2** Semiengorged tick attached to skin (mouthparts embedded) and the characteristic spreading rash of erythema migrans.



**Figure 3** Facial erythema migrans in a man bitten by a tick behind the left ear. We thank the Borreliosis and Associated Diseases Awareness group (BADA), UK, for kindly providing figures 2 and 3.

### EARLY DISSEMINATED LB

Several weeks or months later, a disseminated stage develops when neurological and cardiac involvement occurs. Patients may develop multiple ‘secondary’ EM lesions, usually less than 5 cm in diameter. While the evidence is largely anecdotal, differences in clinical presentations and intensity of the host inflammatory response to Lyme disease appear to be due to different genomic species of *Borrelia*.<sup>11 31 38–42</sup>

Although 18 genomic species are now identified, *B burgdorferi sensu stricto*, *B afzelli* and *B garinii* are recognised as the pathogenic variants in the UK, with *B garinii* the most prevalent pathogenic genospecies in endemic areas. A significant proportion of ticks in the UK carry *Borrelia valaisiana*, which can rarely cause EM.<sup>33 43</sup>

### LATE LB

Late Lyme disease is less common, presenting some years after the initial infection and may involve the joints, skin, central and peripheral nervous system. The diagnosis of late neurological abnormalities has proved the most challenging.<sup>5</sup> Less than 5% of European neuroborreliosis (NB) patients present with late (>6 months to several years) symptoms.<sup>44</sup> Central nervous system manifestations include encephalitis, encephalomyelitis with tetraparesis, tetraspastic syndrome and/or a spastic ataxic gait disorder, cognitive impairment and psychiatric disturbances.

In the UK, NB is the most common complication. Presenting features include meningitis, myeloradiculitis, cranial neuropathies and mononeuritis multiplex. A study of 88 serologically confirmed cases, in south-west England, revealed 22 (25%) had neurological symptoms beyond headache. Fourteen had facial

palsy, eight confusion or drowsiness, four meningism, five radiculopathy, two had sixth nerve palsies and two had peripheral nerve palsies.<sup>37</sup> An Irish study reviewed 30 acute cases; 15 (50%) with neurological symptoms, 12 (80%) with painful radiculopathy and 7 (46%) with cranial neuropathy.<sup>45</sup>

If untreated, around 10% of people will develop acute NB with most (around 95%) presenting acutely within 12 weeks of infection. In adults, the most common presentation is a painful meningoradiculitis. In children, the commonest neurological presentation is facial palsy with a prevalence of between 55% and 71%.<sup>46–47</sup> This is followed by other cranial nerve palsies and/or lymphocytic meningitis, with headache as a prominent feature. North American studies indicate facial nerve involvement in around 60% of adult cases (bilateral in 40%) and abducens nerve in 10%.<sup>48–49</sup> A recent UK study reported a lower prevalence of cranial nerve palsy of only 4.6%.<sup>16</sup> Rarely, individual case reports have described acute transverse myelitis, optic neuritis, recurrent laryngeal nerve palsy, cerebral vasculitis and stroke.<sup>50</sup>

Regardless of the presentation, NB can be 'microbiologically' cured in virtually all patients, using standard 2–4-week intravenous antimicrobial regimens. However, patients with severe manifestations may have a slow or incomplete clinical response.<sup>44–51</sup>

In an overlap between cardiac and neurological complications, postural orthostatic tachycardia syndrome has been described in five patients (all women) previously diagnosed with Lyme disease.<sup>52</sup> The aetiology of dysautonomic sequelae is currently unknown but presumably related to autoimmune factors triggered by exposure to *Borrelia* antigens.

Heart involvement usually involves the conduction system, presenting as atrioventricular block. Cardiac symptoms among patients with Lyme disease in the UK (20% infected in North America and 46% in Europe) are low, reported in 7.7% of cases.<sup>16</sup> Some US reports suggest symptoms can occur in up to 87% of cases of Lyme carditis.<sup>53</sup> Patients with heart involvement may recover without antibiotic prescription although antibiotics are rarely withheld.<sup>54</sup> Patients may present with palpitations, syncope or collapse. Heart block is usually reversible within a few days (median 3 days, range 1–7 in children in New England).<sup>55</sup> In a meta-analysis of 105 American and European patients, the frequency of heart block was similar between American and European patients; 12% with first degree, 16% second degree and 49% with third degree.<sup>56</sup> European and Scandinavian estimates for heart involvement lie between 1% and 10% of cases.<sup>57–59</sup> In support of *borrelia* as a cause of myocarditis, spirochaetes have been demonstrated in cardiac biopsies and within myocardial capillaries from patients with Lyme positive serology.<sup>60–62</sup> Only one case of fatal 'probable' Lyme carditis appears in the UK literature: a 31-year-old farm worker dying suddenly with features of inflammatory pancarditis and complete heart block.<sup>63</sup> A case from the USA has also confirmed *B burgdorferi* DNA, in myocardial tissue, in a young male dying with a diffuse carditis.<sup>64</sup> In Sweden, an increased frequency of sudden death has been noted in young orienteering participants in whom myocarditis was a common feature. *B burgdorferi* may have been responsible,<sup>58</sup> although Bartonella and Chlamydial infections have also been implicated.<sup>65–67</sup>

Wesslen *et al* suggested that Bartonella-induced silent subacute myocarditis, eventually leading to electric instability, was behind these sudden unexpected cardiac deaths.<sup>68</sup> A further possibility is that co-infections are transmitted by the same tick bite, and their pathological synergism exacerbates Lyme disease or induces similar clinical features.<sup>69</sup>

The evidence for confirmed cardiomyopathy is extremely rare in the UK. Despite this, determining *borrelia* serology status in patients with dilated cardiomyopathy and heart block is recommended,<sup>70</sup> although seropositivity for *Borrelia* does not confirm LD as the cause.<sup>71–72</sup>

Opinion remains divided on the role of *borreliae* in cases of chronic 'idiopathic' dilated cardiomyopathy (IDC).<sup>59–73–74</sup> Stanek *et al* demonstrated positive *B burgdorferi* serology in 26.4% of 72 patients with IDC.<sup>75</sup> In a separate study, antibodies to *B burgdorferi* were also reported in 32.7% of 54 consecutive patients with chronic heart failure.<sup>76</sup>

Reports of an aetiological role for *Borrelia* in dilated cardiomyopathy that appeared in the early 1990s<sup>75–76</sup> may have been influenced by a high background seroprevalence. This is illustrated by a greater than 50% seroprevalence in Austrian deer hunters of more than 50 years of age.<sup>77</sup>

A study of 97 British patients found no serological evidence to implicate *B burgdorferi* in the pathogenesis of IDC.<sup>78</sup> A Dutch study that performed PCR analysis on multiple myocardial samples from 37 patients with end-stage dilated cardiomyopathy also found no evidence of microbial presence or persistence.<sup>79</sup>

Lyme arthritis formed the major feature described in the historical cluster of cases,<sup>80–81</sup> but is now appreciated to be less common.

Initial musculoskeletal features accompany, or occur soon after, the onset of EM, with symptoms including fatigue, myalgia, arthralgia and fever.<sup>8</sup> The arthritis has two distinctive patterns, palindromic and chronic persistent form.<sup>82</sup>

The palindromic form affects approximately 60% of patients,<sup>8</sup> typically with an asymmetric oligoarthritis or monoarthritis of large joints, commonly the knees and or ankles.<sup>82–83</sup> Joint effusion is a common presentation and may be out of proportion to the pain experienced.<sup>31</sup> Ankles and wrists are the next most commonly affected sites.<sup>83</sup> Examination reveals warm swollen joints with mild discomfort on movement. The arthritis lasts several weeks or months and tends to be self-limiting.<sup>84</sup> If untreated with antibiotics, frequent recurrence is characteristic, especially in the first few years of the disease.<sup>83–85</sup> Between recurrences, patients are often well with no joint symptoms. A recent case describes a patient declining antibiotics for 4 years who experienced recurrent episodes of arthritis.<sup>85</sup> Patients with untreated Lyme arthritis experience arthritis for longer period (median 43 months, range 4–76), compared with patients undergoing antibiotic-responsive therapy (median 4 months, range 1–51).<sup>86</sup> Joint aspirate shows an elevated level of white blood cells and is negative on culture.<sup>8</sup> Some HLA haplotypes (DR2 and DR4) are more prone to post-treatment antibiotic refractory arthritis,<sup>87–88</sup> and take longer to settle than those who do not possess these alleles.<sup>87</sup>

Radiographs of patients are initially normal, but later radiographic changes resemble those of other causes of inflammatory joint disease. The commonest radiological abnormality is that of knee joint effusions. Soft tissue swelling and thickening or calcification of the entheses also occur. In the later stages, periarticular osteopenia, cartilage loss and cortical or marginal erosions can arise. Less commonly, secondary features of joint failure occur, with further cartilage loss, subchondral sclerosis and osteophytosis.<sup>89</sup>

Case reports of more unusual musculoskeletal forms of Lyme disease have been reported with both myositis and osteomyelitis described.<sup>90</sup> Patients who are untreated may develop the tertiary phase of this infection, likely suffering an infection triggered auto-immune process.<sup>91</sup>

*Borrelia lymphocytoma* is an uncommon, relatively early presentation (early localised LB) which, if untreated, can persist for some time.<sup>31</sup> It comprises a bluish-red isolated swelling, most often on the ear lobes, but also the nipples or scrotum. An important differential to exclude is cutaneous lymphoma.

Acrodermatitis chronica atrophica, a reddish-violet skin discolouration of the extensor surfaces of the limbs, is an unusual tertiary phase lesion. More controversial has been the proposal of an association among localised scleroderma (morphea), lichen sclerosus et atrophicus and granulomas annulare with *Borrelia* infection.<sup>43</sup>

## DIFFERENCES IN THE CLINICAL PRESENTATION OF LYME DISEASE

While many similarities exist between the European and North American Lyme disease, some differences have emerged, which likely reflect the wider genospecies found in Europe. Multiple EM rashes and chronic arthritis features are more common in the USA than in Europe. In Europe, NB is more common, and most often presents as the triad of Bannwarth's syndrome (cranial neuropathy, lymphocytic meningitis and painful radiculitis). The unusual skin conditions of *Borrelia lymphocytoma* (<1% of cases) and acrodermatitis chronica atrophicans are almost unique to Europe and rare if ever reported in the USA.<sup>18 33 72</sup>

In European infections, there is also suspicion of association between cutaneous B cell lymphoma and borreliosis.<sup>92 93</sup> Overall though, more *B burgdorferi* infections in Europe are asymptomatic or minimally so than in the USA.<sup>31</sup> In addition, Lyme carditis is less common and a chronic neuroborreliosis condition is extremely unusual in Europe relative to the USA.<sup>70</sup>

To date, LB has not been documented in tropical regions of the world, with the disease (in Europe) largely confined within longitudes 35° and 60° north, and up to 1300 metres above sea level.<sup>18 19</sup>

## DIAGNOSTIC TESTS FOR LYME DISEASE

Lyme disease should be considered in people who have had an opportunity of contact with ticks and symptoms and signs suggestive of the early disseminated phase of the disease.<sup>94</sup> Direct detection of *B burgdorferi* by culture or DNA amplification has a limited role in routine clinical practice being used mainly in research. The tests most commonly used clinically assess the presence of antibodies to *B burgdorferi*. Sensitive ELISA screening tests are the usual starting point; however, antibodies may not be detectable in the first 2–4 weeks following infection. The first generation ELISA tests had relatively low specificities of 80%–90%. More recently, C6 antigen-based ELISA tests have demonstrated overall specificities of about 95%. If a screening test gives a reactive or equivocal result, the sample should be tested using a more specific test, usually western blot (using separate IgG and IgM line blots), to confirm the presence of *B burgdorferi*-specific antibodies.

Detection of borreliae by culture or PCR can be performed on skin biopsies, synovial or cerebrospinal fluid and in some cases on cardiac biopsies. Examination can be made for spirochaetes and or PCR analysis can be employed to detect *B burgdorferi* DNA.<sup>95</sup> Importantly, and relevant to ongoing Lyme 'controversies', the latter is unable to distinguish DNA from spirochaetes that are alive, recently killed or no longer viable.<sup>96</sup> In the UK, advice on suspected patients should be sought from the Rare and Imported Pathogens Laboratory at Porton Down (Tel: 01980 612348 or by email to <<Lyme.RIPL@phe.gov.

uk>>). A request form for diagnostic services is downloadable from the HPA website.<sup>97</sup>

## PREVENTION OF LYME DISEASE

Avoidance of tick bites is the best policy in areas where Lyme is endemic. Information for those unfamiliar with ticks should be available for residents and workers in tick endemic areas, including visitors who undertake high risk activities (trekking, orienteering, mountain bike riding). Protective clothing can minimise exposed skin and be light coloured to help identify ticks. The application to skin or clothing of diethyltoluene (DEET)-containing insect repellent is also recommended. In addition, permethrin-containing contact insecticides can be applied to clothing in areas of heavy tick infestation. A regular body search for ticks after potential exposure and early removal as soon as possible are valuable protective measures. Bathing after potential exposure is also recommended. Care should be taken to remove the whole tick and particularly the mouth parts, which can still transmit the disease. Tick bite sites should be examined for 4–6 weeks after exposure to check for EM.<sup>18 19</sup> This rash might occur at a site remote to the suspected location, if an additional unsuspected bite has occurred.

Environmental modifications can include deer fencing and grass mowing to reduce the potential tick burden. In hyperendemic areas in the USA, tick eradication has been attempted with area-wide acaricides. More localised methods are employed at deer feeding stations in which deer enter via a 'gate system' (4-poster method) that applies an acaricide. An organic approach is through the use of domesticated guinea fowl, which are voracious consumers of insects, with a fondness for ticks.<sup>98</sup>

## TREATMENT OF LYME DISEASE

The management of patients with LD involves the use of either oral doxycycline (100 mg twice daily) in adults who are not pregnant amoxicillin (500 mg three times a day) or cefuroxime (50 mg twice daily) for a period of 14–21 days.<sup>33 94</sup> Studies have shown that extending doxycycline treatment from 10 to 20 days, or adding one dose of ceftriaxone to the start of a 10-day course of doxycycline, does not enhance therapeutic efficacy in treating early Lyme disease.<sup>99</sup> Late (symptom duration >6 months) or severe disease, particularly with cardiac or neurological involvement, requires a longer course of intravenous antibiotics. For late NB or rare cases of encephalitis or vasculitis, the recommendations are ceftriaxone (2 g once daily) or cefotaxime (2 g three times a day) for 3 weeks.<sup>50</sup> With cardiac involvement, oral doxycycline is appropriate with intravenous antibiotics reserved for cases requiring temporary pacing. A trial using prolonged courses (90 days) of antibiotics (2 g ceftriaxone intravenous for 30 days followed by 200 mg of doxycycline orally for 60 days or matching placebos) on 107 patients with 'persistent symptoms' from Lyme disease showed no benefit as compared with placebo.<sup>100</sup> In around 15% of patients, a Jarisch–Herxheimer type reaction can develop within 24 h of initiating therapy.<sup>20</sup>

With appropriate antibiotics, the development of chronic heart block is an unusual event. However, conduction system involvement can progress rapidly with a requirement for monitoring and facilities for transvenous pacing and haemodynamic support. Estimates for the requirement for temporary pacing in the USA range from 'infrequent'<sup>55</sup> to over 30%.<sup>20 73</sup>

In a study of 221 patients with early phase LD, adequately treated and without cardiac involvement, there was no evidence for the development of cardiac involvement after several years (mean follow-up was 40.6 months). This finding suggests that

such patients do not need long term surveillance for the development of cardiomyopathy.<sup>101</sup>

Lyme arthritis that persists after antibiotic therapy may be treated with hydroxychloroquine or methotrexate. In NB, minocycline has been proposed as beneficial for its ability to cross the blood–brain barrier, with possible anti-inflammatory as well as antimicrobial actions.<sup>102</sup>

Pregnancy and Lyme disease carry some risk, as with other spirochaetal infections, but prompt use of antibiotics will reduce or eliminate the risk.<sup>103 104</sup>

European guidelines on the management of LB are broadly similar to those of the UK,<sup>18 31 33 50</sup> with minor differences in the antibiotic selected, the dose and treatment duration. A major consideration in Europe is the co-transmission of other infections, many of which are rare in the UK (babesiosis, anaplasmosis and Q-fever). Of particular concern is tickborne encephalitis for which a vaccine is available for high risk areas and occupations.<sup>105</sup> Prophylactic use of antibiotics have also been studied in an attempt to prevent the development of Lyme disease after high-risk tick exposure.<sup>106</sup>

### CHRONIC LYME DISEASE AND A POST-LYME DISEASE SYNDROME

The existence of longer-term aspects of Lyme disease remains the most contentious in any review of the subject.<sup>107–109</sup>

#### CHRONIC LYME DISEASE

Chronic Lyme disease implies that patients suffer symptoms from infection with *Borrelia* that become persistent despite antimicrobial therapy. This term is widely used in North America and increasingly in Europe. Prolonged courses of antibiotics have not shown benefit in randomised prospective trials.<sup>6 70 110</sup> Moreover, other spirochaetal infections (ie, leptospirosis, syphilis or relapsing fever) do not require prolonged or repeated courses of antibiotics. Recently, researchers in the USA reported that cases of recurrent EM in patients who received standard antibiotic treatment might be due to re-infection, rather than any relapse of the initial illness. The study showed that in genotypes of *B burgdorferi* isolates from 17 patients, none of 22 paired consecutive episodes of EM were associated with the same strain of *B burgdorferi*.<sup>111</sup>

Central to these arguments is the question of whether *Borrelia* spirochaetes are capable of surviving antibiotic exposure. Support for this view likens the situation to that of tuberculosis, citing antibiotic resistance and avoidance of host immune surveillance.<sup>112 113</sup> Evidence for this comes from animal studies,<sup>114 115</sup> and from the detection of *B burgdorferi* DNA in the tissues of patients with chronic symptoms related to Lyme disease.<sup>116 117</sup>

Co-infections, including babesiosis and human granulocytic anaplasmosis (HGA), might also contribute to chronic symptomatology. Early Lyme disease sufferers can be infected with HGA in 2%–12% of cases and babesiosis in 2%–40% (in addition to *Borrelia*).<sup>118</sup> Researchers at Yale have recently identified *Borrelia miyamotoi*, a spirochaete related to species of *Borrelia* that cause relapsing fever, in patients in southern New England. Positive results for *B miyamotoi* were found in 3% of 273 patients with Lyme or suspected Lyme, in 14% of 21 patients with unexplained ‘summertime febrile illness’ and in only 1% of 584 healthy patients. The bacterium has been identified in around 2% of ticks that carry Lyme disease.<sup>119</sup>

Notwithstanding these findings, some patients will have incomplete resolution of symptoms due to irreversible tissue

damage incurred prior to treatment, for example, from facial nerve palsy or a chronic arthritic joint problem.

#### POST-LYME DISEASE SYNDROME

Post-Lyme disease syndrome differs in its requirement that patients have received prior adequate antimicrobial treatment for Lyme disease and still experience subsequent subjective symptoms. This syndrome occurs in a minority of cases (<5%). Persistent subjective symptoms include fatigue, musculoskeletal pain and neurocognitive features. This can resemble a chronic fatigue or fibromyalgia-like illness,<sup>50 88 120–121</sup> common to the sequelae of a number of infections.<sup>122</sup> The existence of a ‘post-Lyme disease syndrome’, sometimes in the absence of evidence for prior infection, has come under intense scientific scrutiny and criticism.<sup>106 121 123 124</sup>

A recent European statement paper concluded ‘there are no reliable reports of seronegative late-stage Lyme neuroborreliosis’.<sup>6</sup> Opposing views suggesting extended antibiotic treatment periods to be beneficial are ‘evidenced’ by placebo controlled trials.<sup>125 126</sup> Notwithstanding, misinformation, inappropriate testing and unproven, often very chronic antibiotic treatments are rife in some countries and in the ‘private sector’.<sup>127</sup>

A review of 115 patients referred to an infectious diseases unit in the UK revealed that only 27 (23%) were diagnosed with LD. In all, 22 of 26 patients (85%) who had consulted non-NHS clinics received an incorrect diagnosis of LD and many received multiple and excessively prolonged courses of antibiotics.<sup>128</sup> The same is true of patients presenting in endemic areas of North America where, in one study, only 37% patients referred to a Lyme disease centre had either current or prior evidence of Lyme disease.<sup>129</sup> Studies also report the prominence of psychiatric comorbidity and other ‘psychological factors’ in the presentation and outcome of patients who inaccurately ascribe long-standing symptoms to ‘chronic Lyme disease’.<sup>130</sup>

#### THE MEDICO-LEGAL DEBATE

Two US medical societies, the Infectious Diseases Society of America (IDSA) (with the support of the American Academy of Neurology and The National Institute of Health) is now at loggerheads with the International Lyme and Associated Diseases Society (ILADS), both having developed conflicting guidelines.<sup>118 131</sup> This collision of views has resulted in the IDSA accusing the ILADS camp as being implicit in an ‘axis of evil’, in collaboration with misguided physicians, disreputable laboratories and ‘hysterical internet publicity’.<sup>124</sup> In response, ILADS accuse their opponents of ignoring scientific evidence, exclusionary practices and of commercial conflicts of interest in guideline publication. In addition, they claim the currently accepted commercial testing protocol is insensitive, suggesting many patients with Lyme disease will go undiagnosed.<sup>124</sup> Both camps are firmly entrenched, behind increasing numbers of publications, to support their stance either ‘for’<sup>131–134</sup> or ‘against’ chronic infection.<sup>100 118 135–137</sup> Some publications have critically reanalysed trials arriving at different conclusions.<sup>138</sup>

Caught in the middle of this debacle are patients, now increasingly suspicious of the medical establishment. In the USA, patients are wooed by advocacy groups and subject to medical insurance companies refusing to cover long term antibiotic costs, whether necessary or not.<sup>139 140</sup> The insurers have adopted the stance of the IDSA and assume prolonged symptoms are ‘autoimmune’ in nature and not a result of persistent infection. Many now believe that ‘vested interests’ control the definition, diagnosis and treatment of Lyme disease and may

also exert publication bias. These issues are extensively reviewed elsewhere.<sup>109 121 123 141 142</sup>

### CURRENT CLINICAL RESEARCH

In addition to further attempts to clarify controversies surrounding long term issues with Lyme disease, the main areas of advance are in the fields of diagnostics, treatment and possible vaccination. Current serodiagnostic tests for Lyme disease are less sensitive at detecting the disease at an early stage, prompting attempts to improve the sensitivity and in some cases define specific *Borrelia* genotype from the outset.<sup>143–146</sup>

With clinical outcome after 10–28 days of antibiotic therapy being generally excellent, it has been suggested that future studies could address shorter duration of antibiotic therapy.<sup>147</sup> A recent comparison of 10 versus 15 days of doxycycline treatment for EM showed no compromise in efficacy and a similar frequency of non-specific symptoms at 6 months as in controls.<sup>148</sup>

Despite the recent failure, in 2002, of an Osp-A surface-protein based vaccine (developed and licensed for Lyme disease in 1998),<sup>149</sup> current research continues in the search for a future safe and side effect-free vaccine.<sup>150–152</sup>

### CONCLUSIONS

LB is the commonest zoonosis in the northern hemisphere. It is a multi-system infection that can mimic several other diseases. A strong history of exposure (although only around 50% of people recall a tick bite) and recognised clinical features, usually including EM, are essential to making the diagnosis. Enquiry into travel is important, as many cases are acquired abroad.

There has undoubtedly been a significant increase in the number of cases of LD over the last 20 years even though the disease continues to be under-reported. Lyme disease must be one of a very few diseases that has caused such controversy.

#### Main messages

- ▶ Lyme disease appears to be on the increase in the UK.
- ▶ Many cases are acquired abroad and a history of travel abroad is important.
- ▶ Antibody tests may not be positive in the first 2–4 weeks of infection.
- ▶ Little evidence exists to use antibiotic courses for longer than 2–3 weeks.
- ▶ Views differ markedly regarding the existence of 'chronic state' for Lyme disease.
- ▶ Advice on Lyme disease diagnostics is available from the Rare and Imported Pathogens Laboratory at Porton Down.

#### Current research questions

- ▶ The need for the development of an effective vaccine against Lyme disease.
- ▶ The need for the development of a simple rapid test to determine if a person is infected with Lyme borreliosis.
- ▶ The relevance of co-infections to persistent symptomatology.
- ▶ Further investigation into the 'persistence of symptoms' in patients after effective antibiotic treatment.

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#### Self assessment questions

Answer true (T) or false (F) for the below,

1. A. In neuroborreliosis, facial nerve involvement is the most frequent cranial nerve neuropathy  
 B. Cardiac conduction disease (AV block of any degree) is more common in Lyme disease acquired in the UK than in the USA  
 C. Cardiac conduction disease (AV block of any degree) is usually irreversible once present  
 D. Several reports of fatal, indigenously acquired, Lyme related carditis are now reported in the UK  
 E. Erythema migrans is the most common clinical feature
2. A. Seropositivity for Lyme borreliosis is confirmation that the clinical features are due to *Borrelia* infection  
 B. Erythema nodosum is a frequent accompaniment in the first phase of the disease  
 C. Patients can frequently be totally asymptomatic in the 'early localised phase' of the disease  
 D. Lyme disease is similar to other spirochaete related diseases, including syphilis and Leptospirosis, in usually having three phases to the clinical spectrum  
 E. Acrodermatitis chronica atrophicans is a common late feature of Lyme disease
3. A. Lyme disease was first described in children who had been playing in forested land around the town of Lyme Regis in Dorset  
 B. Multiple secondary erythema migrans lesions are a late feature in the third phase of Lyme disease  
 C. Cardiomyopathy is a common sequelae of Lyme borreliosis infection  
 D. Evidence supports the proposition that 'chronic Lyme disease' is caused by the persistence of *borrelia* after appropriate chemotherapy  
 E. 'Post-Lyme disease syndrome' is similar to the chronic fatigue symptomatology that may follow many other infectious diseases

4. A. Badgers remain the most numerous hosts for ticks in the UK
  - B. Ticks require a dry leaf floor and low humidity to survive
  - C. 'Chronic Lyme disease' and 'post-Lyme disease syndrome' have gained wide support in the private health sector and alternative medicine communities
  - D. Extended courses of antibiotics have shown no benefit in reducing the chronicity of symptoms in patients with prolonged symptomology
  - E. Lyme disease is generally more common in men than in women
5. A. Ticks are unlikely to transmit borreliosis if attached to human skin for less than 72 h
  - B. Lyme disease is usually managed by relatively short courses (14–21 days) of widely used antibiotics, including doxycycline, amoxicillin or cefuroxime
  - C. A Jarisch–Herxheimer reaction occurs in around 15% of patients within 24 h of initiating antibiotic therapy
  - D. Avoidance of highly endemic tick infested areas and the wearing of dark protective clothing is the best policy to avoid contracting the disease
  - E. Knee and ankle joints are the most common targets in Lyme arthritis

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## Review

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## Answers

1. A (T); B (F); C (F); D (F); E (T)
2. A (F); B (F); C (T); D (T); E (F)
3. A (F); B (F); C (F); D (F); E (T)
4. A (F); B (F); C (T); D (T); E (T)
5. A (F); B (T); C (T); D (F); E (T)



## Lyme disease in the United Kingdom

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