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REVIEW

The epidemiology, prevention, investigation and treatment of Lyme borreliosis in United Kingdom patients: A position statement by the British Infection Association

British Infection Association

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Summary This paper is a position statement of the British Infection Association on the epidemiology, prevention, investigation and treatment of Lyme borreliosis in United Kingdom patients. It is written to help patients and their doctors to understand the present state of knowledge concerning Lyme borreliosis and to attempt to allay the anxiety that is sometimes associated with this disease.

Lyme borreliosis: a position statement of the British Infection Association

This article sets out the position of the British Infection Association (BIA) on the investigation, diagnosis, treatment and prevention of Lyme borreliosis (Lyme disease) in United Kingdom patients. It is the intention of the Association to provide assistance to patients and their doctors in an area of infectious diseases that is associated with considerable emotion, media and political interest as well as occasionally unorthodox and non-evidence-based clinical or laboratory practice. This paper draws on the experience of UK infectious diseases physicians and medical microbiologists and has taken full account of extant national and specialist societies' guidelines and the evidence on which they are based, from the Czech Republic,[1] Denmark,[2] Finland,[3] France,[4] Germany,[5,6] Netherlands,[7] Norway,[8] Poland,[9] Slovenia,[10] Sweden,[11] Switzerland,[12] and the USA.[13,14] Account was also taken of the report of a Lyme Disease Review Panel of the Infectious Diseases Society of America (IDSA)[15] and the report of an independent panel commissioned by the Health

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Protection Agency (HPA), which reviewed the 2004 guidelines of the International Lyme and Associated Diseases Society (ILADS).[16] A number of recently-published peer-reviewed articles have also been included. This paper has been written with the full involvement of the BIA membership through a consultation process.

Background

Lyme borreliosis (Lyme disease) is the most common human tick-borne infectious disease in the northern hemisphere, occurring predominately in temperate regions of North America, Europe and Asia. It is endemic in many parts of the United Kingdom, particularly in woodland and heathland areas, and occasional cases are acquired in peri-urban parks and recreational areas with suitable habitat. Over 1000 serologically confirmed infections are reported annually in the UK and it has been estimated that there may also be between 1000 and 2000 unconfirmed cases per year. Of the 1000 confirmed, 15-20% is known to have infection which was acquired abroad.

Lyme borreliosis is a spirochaete infection caused by pathogenic genospecies of the *Borrelia burgdorferi* sensu lato group, including *B. burgdorferi* sensu stricto, *Borrelia garinii, Borrelia afzelii, Borrelia bavariensis,* and *Borrelia spielmanii*. Several other non-pathogenic genospecies also occur. All pathogenic genospecies can cause erythema migrans (EM), which is the classical target rash with central clearing that is characteristic of Lyme disease but atypical appearances also occur. The organisms can disseminate to other organs and tissues and cause complications that most commonly affect the nervous and musculoskeletal systems.

There is some evidence that the different pathogenic genospecies can cause variations in manifestations of disseminated disease. *B. burgdorferi* sensu stricto is particularly associated with arthritic and neurological complications, *B.garinii* with neurological presentations and *B. afzelii* with the uncommon late skin manifestation, acrodermatitis chronica atrophicans (ACA) and an associated peripheral neuropathy, but these are not absolute distinctions.

There are worldwide geographical variations in distribution of the different genospecies, which in turn can affect the distribution of disseminated disease presentations. *B. burgdorferi* sensu stricto is the only pathogenic species identified in North America. It also occurs in Europe but is less prevalent in most regions than *B. garinii or B. afzelii,* the two major European pathogenic genospecies. All are present in the UK, and *B. garinii* appears to be the most prevalent pathogenic genospecies in most endemic areas of the country. A significant proportion of infected ticks in the UK carry *Borrelia valaisiana,* which only rarely causes erythema migrans.

The vectors are a number of closely-related, hard-bodied ixodid ticks (*Ixodes ricinus* complex) the life cycles of which include larval, nymphal and adult stages, each requiring a single blood feed. The feeding hosts include small and large mammals and birds. Many small and medium-sized mammals and ground-feeding bird species can be reservoir-competent hosts for *B. burgdorferi* sensu lato. Ticks that acquire borreliae during the course of one feed can maintain infectivity and transmit the organisms to a subsequent host. Humans can be incidental hosts for ticks at any stage of their life cycle but in practice human borrelial infection occurs mainly during nymphal feeds.

The species of tick, the feeding host species, borrelial genospecies and carriage rates of borreliae in ticks all vary according to the geographical location. Human residential, occupational and recreational risk factors are also important in contributing to differing disease incidences and varying clinical manifestations in different parts of the world.

Domestic pets uncommonly show clinical signs of Lyme borreliosis. Seropositivity in dogs living in endemic areas is well recognised in American and European studies. Cats rarely develop clinical disease. Doxycycline is usually an effective treatment in domestic animals.

Clinical manifestations

Clinical case definitions for European Lyme borreliosis have recently been updated[17] and guidelines for diagnosis and treatment of European neuroborreliosis were published in January 2010.[18] Both documents discuss in detail the clinical presentations of Lyme borreliosis and appropriate application of laboratory tests in support of a diagnosis. Numerous other studies and evidence-based guidelines which were published in previous years also address these issues and have been reviewed as part of the development of the BIA's position paper.

B. burgdorferi infection can be asymptomatic. Symptomatic infection (Lyme disease) is potentially progressive and the clinical course has customarily been considered in three stages: early localised, early disseminated and late disease. These are not clear-cut phases and should be regarded as a process that progresses to late disease only in a minority of untreated or inadequately-treated patients.

There is a variable incubation period from a few days to about a month followed in most cases by a typical expanding, homogeneous, annular or target-like erythematous rash, termed erythema migrans (EM), centred on the bite. Untreated, this can last for some weeks or months but eventually resolves. It usually clears within a short time following appropriate antimicrobial treatment. In European prospective studies EM was shown to occur as the presenting sign in about 90% of patients with Lyme borreliosis and can be accompanied by "viral-like" ("flu-like") symptoms including myalgias and arthralgias without significant respiratory involvement. The remaining 10% presented as neuroborreliosis (5-8%), arthritis and other manifestations.

Classical erythema migrans may evolve from a more homogeneous erythematous rash, similar in appearance to a non-specific cellulitis. It is also worth noting that there are other, more common, causes of annular rashes (e.g. ringworm) and some insect bites may present in this way. Furthermore, the classical descriptions of EM were derived from rashes of longer duration than those often presenting to clinicians today and early rashes tend to be more homogeneous than older rashes. EM associated with *B. garinii* may be more homogeneous and intensely erythematous than that associated with *B. afzelii*.

Borrelial lymphocytoma is another presentation of early localised infection. It is uncommon in Europe (<1% of cases) and rarely, if ever, occurs in North America. It usually appears on the earlobe, nipple or scrotum and is characterised by a localised bluish-red nodule or plaque which has an intense lymphocytic infiltrate on histology and can be mistaken for a cutaneous lymphoma. It resolves following appropriate antimicrobial treatment.

Borreliae can disseminate haematogenously or directly to other organs and tissues, causing general systemic symptoms and signs and involving one or more organ systems, mainly the nervous system (facial and/or other cranial palsies, meningitis, meningoradiculitis or a more slowly developing painful radiculopathy), joints (intermittent mono- or oligoarthritis usually affecting the knee or other large joints) and, rarely, the heart (myopericarditis, usually presenting with atrioventricular conduction defects). Multiple EM lesions may also occur following haematogenous spread to other areas of skin. They are usually smaller and more irregular than primary EM lesions. Other rare manifestations include uveitis and tendonitis.

The natural course of untreated borreliosis

Some patients with previously untreated infection can develop features of late-stage disease, months or years later. These late manifestations can affect the skin, musculoskeletal or nervous systems.

Lyme arthritis usually affects the knee, with synovitis, effusion and pain. Effusion is commonly a striking presenting feature, out of proportion to the degree of pain experienced. Patients have usually had earlier intermittent episodes of arthritis before the condition becomes persistent. Lyme arthritis is particularly associated with infections acquired in the USA and in some focal areas of Europe as it occurs mainly in patients with *B. burgdorferi* sensu stricto infections. The condition has become less common in recent years because of better recognition and treatment of Lyme borreliosis at earlier stages of infection.

Steere and Angelis reported follow up data of a cohort of 21 patients with EM and Lyme arthritis over at least 4 years and in whom no antimicrobials were used as treatment. The median total period for episodes of arthritis was 43 months (range 4-76 months) for this cohort compared to a median of 4 months (range 1-51 months) in 50 patients with antimicrobial-responsive arthritis and a median of 16 months (range 4-73 months) in 62 patients with antimicrobial-refractory arthritis .[19] It is possible, therefore, that, although most Lyme arthritis cases will resolve over a period of months or years as the immune system eliminates bacterial antigen from the joint, the use of antimicrobials reduces this duration even in apparently antimicrobial-refractory cases and thereby reduces the overall tissue damage.

Late neurological sequelae of untreated infection include a chronic encephalomyelitis, which can present with clinical features resembling multiple sclerosis, but without the characteristic MRI findings of MS. Some patients, usually in older age groups, present with a painful radiculopathy of gradual onset, developing over many months following infection. European neurologists, who saw a lot of untreated disease in the years before the spirochaetal cause was determined, estimated that the MS-like syndrome occurred in fewer than 1 in 1000 cases of untreated Lyme borreliosis.[20] Use of antimicrobials reduces the risk of this complication. Antimicrobials also give rapid relief to pain and prevent prolonged pain in patients who have radiculopathy.

Acrodermatitis chronica atrophicans (ACA) is an uncommon late cutaneous manifestation causing longstanding bluish-red lesions usually on extensor surfaces of limbs, which may become atrophic and can be accompanied by a peripheral neuropathy. It usually affects older adults, predominantly women. It appears to be associated mainly with *B. afzelii* infections and has only very rarely been reported in American-acquired infections (i.e. with *B. burgdorferi* sensu stricto).

Laboratory tests for the diagnosis of Lyme borreliosis (Table 1)

Laboratory support is not required for a confidently-made, clinical diagnosis of erythema migrans. It should, however, be sought for all later manifestations of Lyme borreliosis, as the clinical features of disseminated and late disease are not specific to the infection.

Direct methods

Culture for *B. burgdorferi* is not available as a routine diagnostic test. It requires specialist media that can be difficult to standardise. The incubation of cultures can take 2-6 weeks, so results are not available in a clinically useful time period. It has a success rate of about 70% on skin biopsy material from EM and is useful for research purposes in providing isolates of proven pathogenicity.

Detection of borrelial DNA by polymerase chain reaction (PCR) is diagnostically useful in certain well-defined circumstances. It is about 70-80% successful in biopsy material from EM, and over 90% in tissue from patients with ACA. It is useful in assessing infection activity in synovial fluid or tissue from patients with suspected Lyme arthritis. It is of only limited value in the investigation of suspected neuroborreliosis as borrelial DNA is detectable in CSF of only 10-30% of patients with proven acute neuroborreliosis, even under optimal circumstances. PCR is not recommended for testing urine or blood samples.[12,21,22]

Serological diagnosis of Lyme

Serological testing for antibodies to *B. burgdorferi* remains the mainstay of diagnostic testing. There have been significant improvements in antibody testing in recent years, including the development of recombinant and synthetic peptide antigens. All serological tests should be undertaken by appropriately-accredited diagnostic laboratories, using validated and preferably CE-marked methods applied in accordance with internationally-accepted recommendations.

A two-stage approach is currently utilised, using a sensitive enzyme immunoassay as a first (screening) step. Screening EIA tests can give false-positive reactions in the presence of other spirochaete infections including syphilis, and other infections

Table 1 Appropriate Laboratory Investigations for Suspected Borrelial Infections (after Stanek G. et al., 2011).[17]

Clinical presentation	Serology	PCR	Notes
Asymptomatic with history of tick exposure or bite	Not indicated	Not indicated	Antibody screening not useful.
Erythema migrans (EM) with reliable history of tick exposure or bite	Not indicated	Not indicated	Early Lyme is serologically positive in 30-70% at presentation. Antibody response may be further delayed or abrogated in patients who have received empirical treatment
Atypical rash with reliable history of tick exposure or bite	Single serum test (30-70% positive on initial test) or paired serum for seroconversion or rise in antibody titre	On expert advice	Paired serology 2-4 weeks apart. PCR 70-80% positive (not required if serological diagnosis made).
Lyme arthritis with reliable history of tick exposure	Single serum IgG test	Occasionally in synovial fluid on expert advice	High specific IgG antibody levels occur in serum. Granulocytic cell response in synovial fluid. PCR of synovial fluid may be useful in antibiotic-refractory arthritis.
Early Lyme neuroborreliosis	Single serum test (>80% positive at presentation) or paired sera for seroconversion or rise in antibody titre. Intrathecal specific antibodies and specific CSF/serum antibody index.	Occasionally in CSF on expert advice	Lymphocytic CSF pleiocytosis is characteristic. Seroconversion within 2-3 weeks of initial seronegativity. PCR of CSF positive in only 10-30% of acute neuroborreliosis.
Late Lyme neuroborreliosis	Single serum IgG test. Intrathecal specific antibodies and specific CSF/serum antibody index		Lymphocytic CSF pleiocytosis is usual. Raised CSF total protein and oligoclonal bands. PCR of CSF is rarely positive
Lyme carditis	Single serum test (>90% positive at presentation) or paired sera for seroconversion or rise in antibody titre	Not indicated	Seroconversion occurs within 2-3 weeks of initial seronegativity
Borrelial lymphocytoma	Single serum test (>90% positive at presentation) or paired sera for seroconversion or rise in antibody titre	Of tissue	PCR of tissue positive in about 80% of untreated cases. Histological analysis useful but not diagnostic
Acrodermatitis chronica atrophicans (ACA)	Single serum IgG test	Of tissue	Very high IgG antibody levels characteristic. PCR of tissue positive in >90% of untreated cases. Histological analysis useful but not diagnostic

including glandular fever, and also when sera from patients with autoimmune disorders and other inflammatory conditions are tested. Samples giving reactive or equivocal results in screening tests should be further investigated in second-stage immunoblot (Western blot) tests. These allow a more detailed evaluation to assess likely reaction specificity, but properly validated interpretive criteria must be applied to ensure maximum specificity is obtained.

Appropriate use of immunoblots greatly increases specificity. Even so, IgM immunoblots remain problematic, as false-positive reactions can still occur in the presence of other acute infections and with autoimmune conditions. Use of IgM tests should be reserved for patients who have acute presentations and with a high probability of Lyme borreliosis. It is important that laboratories are provided with appropriate clinical details, including onset date of illness and date of most recent tick exposure in order to avoid unnecessary and possibly detrimental IgM testing.

Negative results do not exclude a recently acquired infection as an antibody response can take some weeks to develop and may be abrogated if the patient receives early treatment. About 80% of patients with early neuroborreliosis are seropositive at the time they present with neurological symptoms and almost all neuroborreliosis patients who were initially seronegative develop detectable antibodies within several weeks of presentation. Patients with late neuroborreliosis, Lyme arthritis and ACA are almost always very strongly seropositive with reactions to a wide range of antigens apparent on IgG immunoblots.

In response to concerns regarding the diagnosis of "seronegative chronic Lyme disease" the authors of the updated European case definitions conducted a literature search for case reports of seronegative late-stage Lyme borreliosis (LB). They concluded: "*Seronegative late LB, if it occurs at all, is extremely rare and there have been only two reported cases of apparently seronegative ACA and one of seronegative Lyme arthritis in immunocompetent patients. There are no reliable reports of seronegative late-stage Lyme neuroborreliosis.*"[17]

The clinical significance of a positive result should be interpreted in the light of the presenting features of the patient's illness. For example, in patients with high levels of exposure to ticks (e.g. forestry workers) a positive IgG result may reflect past exposure unrelated to a current clinical problem. Seropositivity persists indefinitely in some patients and does not *per se* indicate continuing disease or a need for re-treatment.

The timing of serological tests

Most patients would be seropositive within 2-4 weeks of the onset of systemic symptoms and may be positive on presentation. If the first sample is negative and there is a clinical suspicion of Lyme, then retesting in 2-4 weeks may be useful. For patients who are insistent on being tested following a tick bite but are not showing clinical features of Lyme, testing may be carried out but no sooner than at 8 weeks following the start of the exposure risk. In such cases, it should be explained to the patient that any negative result relates only to that specific exposure and not to a subsequent, possibly inapparent, exposure. Occasionally, a patient without a history of tick exposure or without symptoms and signs suggestive of *B. burgdorferi* infection may be so anxious about Lyme disease that a negative serology test might help to reassure. In such cases, it is advisable for the physician to discuss the case with an appropriate specialist. For all Lyme serology test requests, the request form should carry appropriate details including symptoms, signs, date of onset and tick bite history.

Serological testing for Lyme borreliosis should NOT be undertaken for asymptomatic patients, (including screening of those who have visited endemic areas), or for patients who have had tick bites in the absence of clinical features of Lyme. A patient who has a good history of a tick bite or of recent exposure to ticks, and presents with a typical EM does not require laboratory diagnostic testing. The results of such tests can be clinically misleading, as antibody tests may be positive in only 30-70% of patients at this early stage of infection, due to the relatively slow development of the antibody response.

Serological testing can be useful for patients in whom erythema migrans is suspected but whose rash has atypical features. They may require paired testing on samples taken two to four weeks apart. Differential diagnoses include cellulitis, insect bite or tick bite reactions, ringworm, granuloma annulare, or erythema multiforme.[17]

Tests to be avoided

In the United Kingdom laboratory investigations for Lyme borreliosis should utilise tests which have been properly validated for performance and interpretation and should be undertaken by diagnostic laboratories with a recognised and appropriate accreditation standard. This is particularly important as laboratories offering tests not fulfilling these requirements can provide results that are potentially harmful to patients who are concerned that they may have Lyme disease or a post Lyme syndrome.[23,24]

There is no role for the microscopic examination of blood or other body fluids for *B. burgdorferi* spirochaetes. CD-57 tests are not useful in the diagnosis of Lyme, and lymphocyte transformation tests single-stage immunoblot tests or immunoblots interpreted using non-standardised criteria are not recommended. Various unvalidated EIA tests (e.g. for "blood-brain barrier antibodies") are offered by certain commercial 'Lyme-specialty' laboratories and these are to be avoided.[17,18,21,22,24–26]

Prevention of Lyme borreliosis

Primary prevention

This consists of raising public and health care professionals' awareness of infection risks associated with tick bites and avoidance of habitats which support the tick life cycle. If this is not possible, tick bite risk can be minimised by wearing clothing with sensible coverage such as long sleeved shirts and trousers tucked into socks, and

the use of DEET-containing skin insect repellents. The application of permethrin-containing contact insecticides to clothing can be helpful for people who have heavy and prolonged exposure to ticks, such as forestry workers. Agents containing permethrin should not be applied directly to skin.

Secondary prevention

This involves checking the whole body daily for attached ticks during the period of exposure, especially the skin folds, including armpits, waistband area, groins, backs of knees. The head and neck areas of young children, including scalp should be checked carefully, as tick bites disproportionately occur in these areas in small children, and can easily be missed. Most ticks do not carry infection, and infected ticks do not transmit spirochaetes in the first few hours of a feed. A thorough check at the end of a day in a tick-infested environment is particularly valuable. Attached ticks should be removed using fine-toothed tweezers, pulling gently upwards. Also available from some veterinary surgeries and pet suppliers are tick removal devices. Noxious substances such as alcohol, petrol, volatile oils or lighted cigarette butts or matches should not be applied to the tick because of the risk of skin damage. The area of the tick bite should be disinfected following tick removal to reduce the risk of pyogenic infection. Individuals who have had ticks removed should check for possible development of erythema migrans or other early symptoms for the following four to six weeks, and be aware that an erythema migrans rash might occur at another site following an inapparent tick bite.

Antimicrobial prophylaxis

This is not routinely recommended by European authorities but may be used in immunocompromised individuals following a tick bite. In such situations, for adults, a single dose of doxycycline 200 mg orally and for children aged 12 years or over 4 mgs/kg (up to 200 mg) can be given. Some European authorities recommend post-tick bite prophylaxis for immunosuppressed individuals with single dose of doxycycline or, if contraindicated, a course of amoxicillin. Some authorities also recommend post-tick bite prophylaxis with amoxicillin for pregnant women, but there are no trial data to guide the dose or duration of amoxicillin prophylaxis.

Prophylaxis is recommended in certain limited circumstances in the USA: namely for adults and children over the age of eight years in whom doxycycline is not contraindicated, who sustained adult or nymphal tick bites of duration estimated as $>$36 h (either based on the engorgement of the tick or certainty about duration) in an endemic area in which tick infection prevalence is $>$20% and in whom prophylaxis can be given within 72 h of tick removal. Prophylaxis with amoxicillin is not recommended by American guidelines because there are no trial data to show the efficacy of amoxicillin prophylaxis and it is likely that a multi-day course would be necessary. This has an increased risk of side effects. Also, the excellent efficacy of treatment of Lyme disease if infection were to develop and the very low risk of serious Lyme disease with late sequelae in a person who has received a tick bite, counsels against amoxicillin prophylaxis.

In the USA infection is exclusively caused by *B. burgdorferi* sensu stricto and transmitted by *I. scapularis*. Evidence from various trials including a post-exposure prophylaxis trial in Westchester County, an area of high endemicity, showed that transmission is unlikely to take place within the first 36 h of attachment, so there is a longer lag phase and window of opportunity to give post-exposure prophylaxis than in Europe. The study was associated with a relatively high incidence of adverse reactions to doxycycline.[27]

Many more *B. burgdorferi* infections in Europe are asymptomatic or minimally symptomatic than in the USA. *B. afzelii* in particular is widespread in continental Europe and is the least pathogenic of the major strains, though it can cause some systemic disease. Infection rates in ticks in most areas are lower, and there is some evidence that *B. azelii* can be transmitted by *I. ricinus* from about 24 h, so there is a shorter period available for effective prophylaxis. Also, single-dose prophylaxis for people who are regularly exposed can turn into inadequate treatment for infection that may actually have been unknowingly acquired at an earlier exposure. In the UK about 50% of infected ticks in various surveys carry *B. valaisiana* which is regarded as non-pathogenic and will further alter the risk/benefit equation for prophylaxis.

Treatment of Lyme borreliosis (Table 2)

Numerous evidence-based treatment guidelines have been published by European[1-12] and American[13,14] societies and expert groups. There is broad overall agreement between the guidelines in regard to treatment recommendations, with only minor differences with regard to antimicrobial agents, doses, and treatment durations.

Erythema migrans, early localised and early disseminated borreliosis (without cardiac or neurological manifestations) and borrelial lymphocytoma

First line antimicrobial agents

Recommendations for first line treatment from the USA and most European nations specify doxycycline or amoxicillin. Both have proven efficacy; doxycycline is also effective against anaplasmosis, an uncommon ixodid tick borne infection, which can be a co-infection with Lyme borreliosis. Some countries (particularly in Scandinavia) recommend high-dose oral penicillin V in preference to amoxicillin because of its narrower spectrum of activity, but amoxicillin is the preferred beta-lactam agent in the United Kingdom because of its superior absorption. Most guidelines do not recommend the use of parenteral agents as first-line treatments for patients with early Lyme disease without neurological or cardiac involvement, because they have not been shown to be superior to oral agents. They can also cause serious adverse effects and are expensive. Third generation cefalosporins, in particular ceftriaxone, are recommended

Table 2 Suggested Antimicrobial Treatment Regimens (based on French guidelines[4] and EFNS guidelines of Mygland A et al. [18]).

Clinical condition	Antimicrobial[a]	Regimen	Duration *(d)*	Children < 12y[b]	Pregnancy or breastfeeding	Notes
a) Erythema migrans b) Early localised Lyme c) Early disseminated Lyme (no cardio or neuro signs) d) Borrelial lymphocytoma e) Asymptomatic Lyme carditis	1st line: doxycycline or amoxicillin 2nd line: cefuroxime axetil 3rd line: azithromycin	100 mg bd po 500 mg tds po 500 mg bd po 500 mg od po	14—21 14—21 14—21 10	1st line: amoxicillin 2nd line: cefuroxime axetil 3rd line: azithromycin	1st line: amoxicillin 2nd line: cefuroxime axetil 3rd line: azithromycin	Azithromycin requires careful monitoring for treatment failure
Lyme carditis with: a) 1st degree block + prolonged (≥ 300 ms) PR interval b) 2nd or 3rd degree block	Ceftriaxone	2g od iv	14—21	Ceftriaxone	Ceftriaxone	IDSA advises ceftriaxone to be switched to oral doxycycline or amoxicillin when pacing or iv access no longer required
Neuroborreliosis: a) Isolated facial nerve palsy	Doxycycline or amoxicillin	100 mg bd po 500 mg tds po	14—21 14—21	Amoxicillin	Amoxicillin	EFNS advises 14d adequate in acute neuroborreliosis
b) Meningitis without encephalitis, myelitis or vasculitis	Doxycycline	100 mg bd po	14—21	Ceftriaxone	Ceftriaxone	
c) Meningitis with encephalitis, myelitis or vasculitis	Ceftriaxone	2g od iv	14	Ceftriaxone	Ceftriaxone	
d) Late neuroborreliosis	Ceftriaxone	2g od iv	14—28	Ceftriaxone	Ceftriaxone	
Lyme arthritis	1st line: doxycycline 2nd line: amoxicillin	100 mg bd po 500 mg tds po	21—28 21—28	Amoxicillin	Amoxicillin	
Refractory Lyme arthritis	Doxycycline or ceftriaxone	100 mg od po 2g od iv	30—60 14—21	Ceftriaxone	Ceftriaxone	Antimicrobial-refractory arthritis should be managed by a rheumatologist
Acrodermatitis chronica atrophicans (ACA)	Doxycycline	100 mg bd po	21—28	—	—	ACA occurs predominantly in older adults.

[a] Readers are referred to the British National Formulary for information on cautions, contra-indications, side-effects, and drug interactions, including use in pregnancy and breast feeding.

[b] Doses given are for adults and will require adjustment for children. The durations for adults and children are the same.

as alternative agents for early disseminated Lyme borreliosis in the Czech Republic, Finland and the Netherlands.

Second line antimicrobial agents
Cefuroxime axetil is recommended for patients who are unable to take doxycycline (including children younger than 12y in the UK, 8-9y in Europe, 8y in the US, and pregnant or breast feeding women) or amoxicillin. Clinical trials have shown it to be effective in early Lyme borreliosis but it is more expensive than the other recommended agents, hence most guidelines recommend reserving its use for selected cases. Cefuroxime axetil, being a cefalosporin, will increase the risk of *Clostridium difficile* infection and may have variable and unpredictable absorption.

Third line antimicrobial agents
Macrolides are recommended as third line agents for the treatment of patients in whom beta lactams and doxycycline are contraindicated. Azithromycin is the macrolide of choice because of its high tissue concentrations. Treatment failures can occur with any macrolide, particularly erythromycin. Macrolides should never be first line choices and patients treated with them should be monitored carefully for signs of continuing or recrudescent disease.

Lyme carditis

Patients with symptomatic cardiac involvement, second or third degree heart block or first degree with prolonged PR interval ($>/=300$ ms) should be treated in hospital because of the danger of rapid worsening of heart block. Occasional patients may require temporary pacemaking. Patients not requiring hospitalisation can be treated with oral antimicrobials but those in hospital should receive a third generation cefalosporin such as ceftriaxone. This may be converted to oral doxycycline once pacing or IV access is no longer required for the cardiac condition[13]

Lyme neuroborreliosis

Most American and European guidelines published prior to 2010 recommend the use of ceftriaxone (preferred because of its convenient once-daily dosing) or cefotaxime for two to four weeks for neurological infections. These third generation cefalosporins have good CSF penetration. Parenteral benzylpenicillin or oral doxycycline are recommended as alternatives.

The European Federation of Neurological Societies (EFNS) guidelines published in 2010, recommend that a two-week course of oral doxycycline is non-inferior to a similar duration of parenteral ceftriaxone for adults and children over the age of eight who have acute neuroborreliosis (including meningitis) without evidence of encephalitis, myelitis or vasculitis.[18] This follows the publication in 2008 of the findings of a large double-blind non-inferiority trial performed in Norway.[28]

The EFNS guidelines recommend parenteral ceftriaxone for two weeks for patients with acute neuroborreliosis with encephalitis, myelitis or vasculitis and for three weeks for those with late neuroborreliosis (mononeuropathy, radiculopathy, progressive encephalomyelitis or cerebral vasculitis). Patients with peripheral neuropathy associated with ACA can be treated with doxycycline as per recommendation for treatment of the skin condition.

Patients with isolated facial palsy are usually treated with oral antimicrobials, using doxycycline unless contraindicated. The duration of facial nerve palsy may not be shortened by antimicrobials but treatment is indicated to prevent possible further sequelae.

Lyme arthritis

Oral treatment with doxycycline or amoxicillin for four weeks is adequate for most cases although ceftriaxone is an alternative and should be considered in cases where the arthritis has failed to respond or has worsened following a four week course of oral agents. Non steroidal anti-inflammatory drugs may be used during initial treatment. Intra-articular steroid injections are not recommended unless there is a post-treatment persistence of joint inflammation and synovial fluid and/or synovium biopsies are negative for borrelial DNA in PCR tests. Such persistence, which is termed antibiotic-refractory Lyme arthritis and is thought to have an autoimmune component, should be managed by a rheumatologist. Arthroscopic synovectomy may improve persistent synovitis but is rarely required.

Acrodermatitis chronica atrophicans

No randomised control trials have been performed on patients with this uncommon presentation, but most guidelines recommend 21 to 28 days of oral or parenteral antibiotics.

Treatments that are not recommended

The Infectious Diseases Society of America Review Panel Report[15] states that treatments should be of proven benefit or form part of a properly conducted, scientifically sound and ethics-approved clinical trial. The Report further states that there is evidence that some treatments are ineffective. First generation oral cefalosporins such as cephradine or cephalexin should not be used because there is a proven lack of efficacy. Quinolones, glycopeptides, metronidazole, tinidazole, ketolides, isoniazid, trimethoprim-sulfamethoxazole, fluconazole have few data to support their efficacy and some evidence to indicate their lack of efficacy. Benzathine penicillin G is not a desirable agent because it is given intramuscularly. Carbapenems should be effective but are not recommended unless treatment is intended to cover blindly for other central nervous system bacterial infections.

There is evidence that some treatment strategies can be harmful. These include antimicrobial combinations, pulsed-dosing and long term antimicrobials. There are few data to support the use of other treatments and evidence that they may be harmful, sometimes seriously. These include hyperbaric oxygen, ozone, fever therapy, intravenous immunoglobulin, cholestyramine, intravenous hydrogen peroxide and specific nutritional supplements.[15]

Persistent symptoms following treated Lyme borreliosis; "chronic Lyme disease"

The term "chronic Lyme disease" is not consistently defined. It has been applied to patients with presentations of active, previously untreated, infection, such as late neuroborreliosis or ACA, those who have persistent symptoms following treatment for Lyme borreliosis, patients who have had Lyme borreliosis in the past but whose current illness is unrelated to infection with *B. burgdorferi*, and patients who have no evidence of current or past borrelial infection.[29,30] In prospective and retrospective studies many patients labelled as having "chronic Lyme disease" fell into the last category and had received the diagnosis because poorly-specific case definitions and/or unvalidated, poorly-specific laboratory tests had been applied.[31] The IDSA Guidelines Review Panel reiterated the 2006 USA guidelines' recommendation that, "*Whatever definition is eventually adopted, having once had objective clinical or laboratory evidence of B. burgdorferi infection must be a condition sine qua non until a syndrome is formally defined.*".[15] The BIA shares the view that only a formally-defined syndrome specific for chronic Lyme disease will obviate the need for previous clinical or laboratory evidence of *B. burgdorferi* infection. Until such time, a diagnosis of chronic Lyme disease should not be made without this evidence.

In all cases patients should be carefully evaluated for clinical and laboratory evidence of *B. burgdorferi* infection and any previous treatment history should be reviewed, as some patients with Lyme borreliosis may have been treated previously with inappropriate agents or inadequate doses and require re-treatment. Others, especially those who had longstanding infection prior to treatment, may have slow-to-heal or permanent tissue damage despite microbiological cure, and they require other treatment modalities for symptomatic relief and rehabilitation. A small proportion of patients have persistent subjective symptoms following apparently appropriate treatments for Lyme borreliosis, and without new clinical signs or laboratory evidence of ongoing active infection. Symptoms include fatigue, myalgia, arthralgia, paraesthesia, poor sleep, irritability, and concentration difficulties. These have been termed "post-Lyme symptoms" if of short duration or "post-Lyme syndrome" (PLS) if present for more than six months.[13,17,18,30] Symptoms of PLS appear to be similar to those seen in a minority of patients following other systemic infections (so-called "post-infection" or "post-viral" syndromes) and, again, similar to some other infections, are more likely to be present in patients who had severe presentations in the acute illness.[32] Studies of prolonged antimicrobial treatments of patients with PLS have not shown sustained benefit, and have highlighted significant risks of serious adverse events, including central vascular catheter infections, fungal infections, *Clostridium difficile* enterocolitis and biliary stasis.[30,33,34–37]

Few treatment trials for Lyme borreliosis have incorporated normal control groups, but a recent large Slovenian study of erythema migrans treatment (doxycycline vs. cefuroxime axetil) followed up patients and matched healthy controls for one year.[38] The study showed that both agents are highly effective and the frequency of non-specific symptoms at six and twelve months was no greater in patients than in the uninfected control group. A Swedish prospective treatment and outcome study of paediatric patients with neuroborreliosis also incorporated an uninfected control group and showed good outcomes, with no progressive or new neurological findings in patients and similar rates of non-specific symptoms such as headache and fatigue in patients and controls.[39] Both studies highlight the background prevalence of non-specific symptoms in the general population. The presence of arthralgia, myalgia, fatigue, and other subjective symptoms after treatment for Lyme borreliosis must be evaluated in the context of background complaints in a significant proportion of individuals.

Further research is required into the causes of post-infection syndromes. There is a large volume of anecdotal accounts and poorly-designed studies relating to post Lyme syndromes and "chronic Lyme disease". The IDSA guidelines Review Panel referred to such evidence as "*fertile material for hypothesis-generation, but intrinsically incapable of hypothesis-testing.*".[15] This is a view with which the BIA concurs.

The BIA is particularly concerned that patients with a wide range of conditions including multiple sclerosis, motor neurone disease, autoimmune diseases, arthritis and malignancies have received diagnoses of "chronic Lyme disease" without objective clinical or laboratory support.[30,31,40,41] Many patients have received potentially dangerous treatments, including prolonged courses of antibiotics, antiparasitic and other agents and have lost opportunities for appropriate management of their conditions. The Association recommends that patients presenting with symptoms and history not typical of Lyme borreliosis should be investigated according to good medical practice, and that investigations for Lyme borreliosis should be performed only if there are good clinical and epidemiological indications.

Conclusion

Lyme borreliosis is sometimes associated with much anxiety. There has been a great deal written about this disease, not only in academic journals, but also in the lay media and on the internet. These publications are of variable quality, particularly where there has been no peer-review or similar quality assurance process applied. It can be difficult for patients to judge the value of the available articles and websites and thereby detect and avoid unsubstantiated opinion and advice.

This paper has been written to help patients and their doctors to make sense of the risks of Lyme borreliosis and its appropriate investigation, prevention and treatment through good medical practice. The BIA hopes that this objective will be achieved.

References

1. Vanousova D, Hercegova J. Lyme borreliosis treatment. *Dermatol Ther* 2008;**21**(2):101–9.
2. Dessau R, Bangsborg JM, Ejlertsen TP, Hansen K, Lebech A-M, Ostegaard C. *Ugeskr Laeger* 2006;vol. 168 (Summary)2805–2807.
3. Oksi J, Seppala IJT, Hytonen J. Lymen borrelioosin diagnostiikka ja hoito. *Duodecim* 2008;**124**:1483–91.

4. Societe de Pathologie Infectieuse de Langue Francaise. Lyme borreliosis: diagnostic, therapeutic and preventive approaches. *Med Mal Infect* 2007;**37**(S3):8153—74.
5. *Leitlinien der Deutschen Gesellschaft fur Neurologie*, http://leitlinien.net/; 2008. AWMF Leitlinien-Register Nr 030/071.
6. *Leitlinien der Deutschen Dermatologischen Gesellschaft*, http://leitlinien.net/; 2009. AWMF Leitlinien-Register Nr 013/044.
7. Speelman P, de Jongh BM, Wolfs TF. *CBO Richtlijn Lyme Borreliose*. In: *Ned Tijdschr Geneeskd*, **148**. Wittenberg: CBO, ISBN 90-76906-89-0; 2004 (summary): 659—663.
8. Ljostad U, Mygland A. Lyme-borreliose hos voksne. *Tidsskr Nor Legeforen*:1175—8, www.legemiddelhandboka.no, 2008;**128**. Norsklegemiddelhåndbok for helsepersonell.
9. Flisiak R, Pancewicz S. Diagnosis and treatment of Lyme borreliosis: recommendations of the Polish Society of epidemiology and infectious diseases. *Przegl Epidemiol* 2008;**62**:193—9.
10. Strle F. Principles of the diagnosis and antibiotic treatment of Lyme borreliosis. *Wien Klin Wochenschr* 1999;**111**:911—5.
11. Albage M, Berglund J, Bergman D, Bylund P, Dotevall L, Edlund C, et al. *Lakemedelsbehandling av borreliainfektion—ny recommendation*. Information fran Lakemedesverket 4; 2009: 12—17.
12. Evison J, Aebi C, Francioli P, Peter O, Bassetti S, Gervaix A, et al. Borreliose de Lyme. Diagnostic et traitement de la borreliose de Lyme chez l'adulte et l'enfant: recommandations de la Societe Suisse d' Infectiologie. *Rev Med Suisse* 2006;**2**:919—40.
13. Wormser GP, Dattwyler RJ, Shapiro ED, Halperin JJ, Steere AC, Klempner MS, et al. The clinical assessment, treatment and prevention of Lyme disease, human granulocytic anaplasmosis and babesiosis. Clinical Practice Guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2006;**43**:1089—134.
14. Halperin JJ, Shapiro ED, Logigian E, Belman AL, Dotevall L, Wormser GP, et al. Practice parameter: treatment of nervous system Lyme disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2007;**69**:91—102.
15. Lantos PM, Charini WA, Medoff G, Moro MH, Mushatt DM, Parsonnet J, et al. Final report of the Lyme disease review panel of the Infectious Diseases Society of America. *Clin Infect Dis* 2010;**51**(1):1—5.
16. Health Protection Agency. *An independent appraisal and review of ILADS 2004 'Evidence-based guidelines for the management of Lyme disease' (Professor BI Duerden, Chair). Report presented to HPA* December 2010;**8**. Available at: http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/LymeDisease/GeneralInformation/; December 2010.
17. Stanek G, Fingerle V, Hunfeld K-P, Jaulhac B, Kaiser R, Krause A, et al. Lyme borreliosis: clinical case definitions for diagnosis and management in Europe. *Clin Microbiol Infect* 2011;**17**:69—79.
18. Mygland A, Ljostad U, Fingerle V, Rupprecht T, Schmutzhard E, Steiner I. European Federation of neurological societies guidelines on the diagnosis and management of European Lyme neuroborreliosis. *Eur J Neurol* 2010;**17**:8—16.
19. Steere AC, Angelis SM. Therapy for Lyme arthritis: strategies for the treatment of antibiotic-refractory arthritis. *Arthritis Rheum* 2006;**54**:3079—86.
20. Halperin JJ, Logigian EL, Finkel MF, Pearl RA. Practice parameters for the diagnosis of patients with nervous system Lyme borreliosis (Lyme disease). *Neurology* 1996;**46**:619—27.
21. Aguero-Rosenfeld ME, Wang G, Schwartz I, Wormser GP. Diagnosis of lyme borreliosis. *Clin Microbiol Rev* 2005;**18**(3):484—509.
22. Wilske B, Fingerle V, Schulte-Spechtel U. Microbiological and serological diagnosis of Lyme borreliosis. *FEMS Immunol Med Microbiol* 2007;**49**:13—21.
23. *Chief Medical Officer's Update Autumn* 2009;**49**. 4.
24. Duerden B. Unorthodox and unvalidated laboratory tests in the diagnosis of Lyme borreliosis and in relation to medically unexplained symptoms. Report to the Chief Medical Officer. http://www.dh.gov.uk/assetroot/04/13/89/17/04138917.pdf.
25. Marques A, Brown MR, Fleisher TA. Natural killer cell counts are not different between patients with post-Lyme disease syndrome and controls. *Clin Vaccine Immunol* 2009;**16**(8):1249—50.
26. Anon. Centers for Disease Control and Prevention. Notice to readers: caution regarding testing for Lyme disease. *MMWR* 2005;**54**(5):125.
27. Nadelman RB, Nowakowski J, Fish D, Falco RC, Freeman K, McKenna D, et al. Prophylaxis with single-dose doxycycline for the prevention of Lyme disease after an *Ixodes scapularis* tick bite. *N Engl J Med* 2001;**345**:79—84.
28. Ljostad U, Skogvoll E, Eikeland R, Midgard R, Skarpaas T, Berg A, et al. Oral doxycycline versus intravenous ceftriaxone for European Lyme neuroborreliosis: a multicentre, non-inferiority, double-blind, randomised trial. *Lancet Neurol* 2008;**7**(8):690—5.
29. Feder HM, Johnson BJ, O'Connell S, Shapiro ED, Steere AC, Wormser GP, et al. A critical appraisal of chronic Lyme disease. *N Engl J Med* 2007;**357**:1422—30.
30. Marques A. Chronic Lyme disease: a review. *Infect Dis Clin North Am* 2008;**22**(2):341—60.
31. Hassett AL, Radvanski DC, Buyske S, Savage SV, Sigal LH. Psychiatric comorbidity and other psychological factors in patients with "chronic Lyme disease". *Am J Med* 2009;**122**(9):843—50.
32. Hickie I, Davenport T, Wakefield D, Vollmer-Conna U, Cameron B, Vernon SD, et al. Postinfective and chronic fatigue syndromes precipitated by viral and nonviral pathogens: prospective cohort study. *BMJ* 2006;**333**(7568):575.
33. Klempner MS, Hu LT, Evans J, Schmid CH, Johnson GM, Trevino RP, et al. Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. *N Engl J Med* 2001;**345**(2):85—92.
34. Kaplan RF, Trevino RP, Johnson GM, Levy L, Dornbush R, Hu LT, et al. Cognitive function in post-treatment Lyme disease. *Neurology* 2003;**60**:1916—22.
35. Krupp LB, Hyman LG, Grimson R, Coyle PK, Melville P, Ahnn S, et al. Study and treatment of post Lyme disease (STOP-LD). A randomized double masked clinical trial. *Neurology* 2003;**60**(12):1923—30.
36. Fallon BA, Keilp JG, Corbera KM, Petkova E, Britton CB, Dwyer E, et al. A randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy. *Neurology* 2008;**70**(13):992—1003.
37. Oksi J, Nikoskelainen J, Hiekkanen H, Lauhio A, Peltomaa M, Pitkaranta A, et al. Duration of antibiotic treatment in disseminated Lyme borreliosis: a double-blind, randomized, placebo-controlled, multicenter clinical study. *Eur J Clin Microbiol Infect Dis* 2007;**26**(8):571—81.
38. Cerar D, Cerar T, Ruzic-Sabljic E, Wormser GP, Strle F. Subjective symptoms after treatment of early Lyme disease. *Am J Med* 2010;**123**(1):79—86.
39. Skogman BH, Croner S, Nordwall M, Eknefelt M, Ernerudh J, Forsberg P. Lyme neuroborreliosis in children: a prospective study of clinical features, prognosis and outcome. *Ped Infect Dis J* 2008;**27**(12):1089—94.
40. ALSUntangled Group. ALSUntangled update 1: investigating a bug (Lyme disease) and a drug (Iplex) on behalf of people with ALS. *Amyotroph Lateral Scler* 2009;**10**:248—50.
41. Seidel MF, Domene AB, Vetter H. Differential diagnoses of suspected Lyme borreliosis or post-Lyme-disease syndrome. *Eur J Clin Microbiol Infect Dis* 2007;**26**(9):611—7.