Lyme disease

NICE guideline

Draft for consultation, September 2017

This guideline covers diagnosing and managing Lyme disease. It includes advice on clinical assessment for Lyme disease, which tests to use and when, and treatment with antibiotics. It aims to raise awareness of when Lyme disease should be suspected and ensure that people are given prompt and consistent treatment. It does not cover preventing Lyme disease.

Who is it for?

- Healthcare professionals including GPs, nurses, specialists and microbiologists
- Commissioners and providers
- People with Lyme disease, their families and carers

This version of the guideline contains:

- the draft recommendations
- rationale and impact sections that explain why the committee made the recommendations and how they might affect practice
- the guideline context
- recommendations for research.

Information about how the guideline was developed is on the guideline's page on the NICE website. This includes the evidence reviews, the scope, and details of the committee and any declarations of interest.

Contents

Recommendations

People have the right to be involved in discussions and make informed decisions about their care, as described in your care.

Making decisions using NICE guidelines explains how we use words to show the strength (or certainty) of our recommendations, and has information about prescribing medicines (including off-label use), professional guidelines, standards and laws (including on consent and mental capacity), and safeguarding.

1.1 Awareness of Lyme disease

1.1.1 Be aware that:

- Lyme disease is transmitted by the bite of an infected tick
- ticks are mainly found in grassy and wooded areas, particularly areas that are overgrown, including gardens and parks
- tick bites may not always be noticed
- infected ticks are found throughout the UK and Ireland, and although some areas appear to have a higher prevalence of infected ticks, prevalence data are incomplete
- particularly high-risk areas are the South of England and Scottish Highlands but infection can occur in many areas
- Lyme disease may be more prevalent in parts of central, eastern and northern Europe (including Scandinavia) and parts of Asia, the US and Canada.

1.1.2 Be aware that most tick bites do not transmit Lyme disease and that prompt removal of the tick reduces the risk of transmission.

1.1.3 Give people advice about:

- where ticks are commonly found (such as grassy, wooded and overgrown areas, including gardens and parks)
- the importance of prompt tick removal and how to do this

- covering exposed skin and using insect repellents
- how to check themselves and their children for ticks on the skin
- sources of information on Lyme disease, such as NHS Choices and Public Health England, and organisations providing information and support, such as patient charities.

To find out why the committee made the recommendations on awareness of Lyme disease and how they might affect practice, see rationale and impact.

1.2 Diagnosis

Clinical assessment

1.2.1 Diagnose Lyme disease in people with erythema migrans[1], that is:

- a red rash, that increases in size and may sometimes have a central clearing
- not usually itchy, hot or painful
- usually becomes visible from 1 to 4 weeks (but can appear from 3 days to 3 months) after exposure and lasts for several weeks
- usually at the site of the tick bite.

1.2.2 Be aware that a rash can develop as a reaction to a tick bite, which is not erythema migrans, that:

- usually develops and recedes over 48 hours from the time of the tick bite
- may or may not be hot, itchy or painful
- may be caused by an inflammatory reaction or infection with a common skin pathogen.

1.2.3 Consider the possibility of Lyme disease in people presenting with several of the following symptoms, because Lyme disease is a possible but uncommon cause of:

[1] See NHS choices for an image of erythema migrans.

- flu-like symptoms, such as fever and sweats, swollen glands and fatigue
- neck pain or stiffness
- joint or muscle pain
- cognitive impairment, such as memory problems and difficulty concentrating (sometimes described as 'brain fog')
- headache
- paraesthesia.

1.2.4 Consider the possibility of Lyme disease in people presenting with symptoms and signs relating to an organ system (focal symptoms) because Lyme disease is a possible but uncommon cause of:

- neurological symptoms, such as facial palsy or other unexplained cranial nerve palsies, meningitis, mononeuritis multiplex or other unexplained radiculopathy; or rarely encephalitis, neuropsychiatric presentations or unexplained white matter changes on brain imaging
- cardiac problems, such as heart block or pericarditis
- inflammatory arthritis affecting 1 or several joints
- eye symptoms (less commonly), such as uveitis or keratitis
- skin rashes resembling erythema migrans, acrodermatitis chronica atrophicans or lymphocytoma.

1.2.5 If a person presents with symptoms that suggest the possibility of Lyme disease, explore how long the person has had symptoms and their history of possible tick exposure, for example, ask about:

- activities that might have exposed them to ticks
- travel to areas where Lyme disease is known to be prevalent.

1.2.6 Do not rule out the possibility of Lyme disease in people with symptoms but no clear history of tick exposure.

1.2.7 Do not diagnose Lyme disease in people without symptoms, even if they have had a tick bite.

1.2.8 Be cautious about diagnosing Lyme disease in people without a supportive history or positive testing because of the risk of:

- missing an alternative diagnosis
- providing inappropriate treatment.

1.2.9 Follow usual clinical practice to manage symptoms, for example pain relief for headaches or muscle pain, in people being assessed for Lyme disease.

1.2.10 Be aware that people with Lyme disease may have symptoms of cognitive impairment and may have difficulty explaining their symptoms. Follow the recommendations in NICE's guideline on patient experience in adult NHS services.

To find out why the committee made the recommendations on clinical assessment and how they might affect practice, see rationale and impact.

Laboratory investigations

See also the algorithm for laboratory investigations.

1.2.11 Diagnose and treat Lyme disease without laboratory testing in people with erythema migrans.

1.2.12 Offer testing if there is a clinical suspicion of Lyme disease, using an enzyme-linked immunosorbent assay (ELISA) for Lyme disease that tests for both IgM and IgG antibodies and is based on C6 peptide or an equivalent purified or synthetic VIsE antigen.

1.2.13 If the ELISA is positive or equivocal, offer an immunoblot test to confirm diagnosis of Lyme disease.

1.2.14 If the ELISA for Lyme disease is negative and the person still has symptoms, review their history and symptoms again, and consider whether an alternative diagnosis is likely.

1.2.15 For people with a negative ELISA who were tested within 4 weeks from symptom onset, consider repeating the ELISA 4 to 6 weeks after the first ELISA test if Lyme disease is still suspected.

1.2.16 For people with a negative ELISA who have had symptoms for 12 weeks or more and Lyme disease is still suspected:

- repeat the ELISA **and**
- perform an immunoblot test.

1.2.17 Consider treatment with antibiotics (see section 1.3) before test results become available if there is a high probability that the person has Lyme disease.

1.2.18 If Lyme disease is confirmed with ELISA and immunoblot tests, and the person has focal symptoms, consider a discussion with or referral to an infectious disease specialist or a specialist appropriate for the person's symptoms (for example, an adult or paediatric rheumatologist), without delaying treatment.

1.2.19 If ELISA and immunoblot tests are negative but unexplained symptoms persist, consider a discussion with or referral to an infectious disease specialist or a specialist appropriate for the person's symptoms (for example, an adult or paediatric rheumatologist) to:

- review whether further tests may be needed for suspected Lyme disease, for example synovial fluid aspirate or biopsy, or lumbar puncture for cerebrospinal fluid analysis **or**
- consider alternative diagnoses.

1.2.20 Be aware that some people, particularly those living in high-prevalence areas, may have positive serology but do not have Lyme disease because antibodies can remain in the body for some years.

1.2.21 Carry out tests for Lyme disease only at NHS-accredited laboratories that:

- use validated tests (validation should include published evidence on the test methodology, its relation to Lyme disease and independent reports of performance)
- participate in a formal external quality assurance programme.

1.2.22 When tests have been done in laboratories that do not fulfil the criteria in recommendation 1.2.21, do not diagnose Lyme disease, but carry out testing again using an NHS-accredited laboratory.

To find out why the committee made the recommendations on laboratory investigations and how they might affect practice, see rationale and impact.

Information about tests for Lyme disease

1.2.23 Discuss with the person the accuracy and limitations of the different tests for diagnosing Lyme disease.

1.2.24 Explain to people being tested that most tests for Lyme disease assess for the presence of an immune response (antibodies) to borreliosis infection, and that the accuracy of blood tests may be reduced if:

- testing is carried out too early (before antibodies have developed)
- the person has reduced immunity, which might affect the development of antibodies, for example people on immunosuppressant treatments.

1.2.25 Advise people that tests available privately (including from overseas) may not have been fully evaluated or meet the standards needed to diagnose Lyme disease.

1.2.26 Discuss with people who may have Lyme disease that:

- the symptoms and signs associated with Lyme disease are similar to those for other conditions
- symptoms such as tiredness, headache and muscle pain are common and a specific medical cause is often not found.

To find out why the committee made the recommendations on information about tests, and how they might affect practice, see rationale and impact.

1.3 Management

1.3.1 Follow usual clinical practice for emergency referrals, for example, in people with symptoms that suggest central nervous system infection or complete heart block, even if Lyme disease is likely to be the underlying cause.

1.3.2 Discuss with a specialist, for example a paediatrician, the diagnosis and management of Lyme disease without erythema migrans in children and young people under 18.

To find out why the committee made the recommendations on emergency referral and referral for children and young people, and how they might affect practice, see rationale and impact.

Antibiotic treatment

1.3.3 For adults and young people (aged 12 and over) diagnosed with Lyme disease, offer antibiotic treatment according to their symptoms as described in table 1.

1.3.4 For children (under 12) diagnosed with Lyme disease, consider antibiotic treatment according to their symptoms as described in table 2.

1.3.5 Ask women whether they might be pregnant before offering antibiotic treatment for Lyme disease (see recommendation 1.3.15 on treatment in pregnancy).

1.3.6 If symptoms worsen within the first day of antibiotic treatment, assess the person for Jarisch-Herxheimer reaction.

Table 1: Antibiotic treatment for Lyme disease in adults and young people (aged 12 and over) according to symptoms[a]

Symptoms	Treatment	First alternative	Second alternative
Erythema migrans	Doxycycline 100 mg twice per day or 200 mg once per day for 21 days	Amoxicillin 1 g 3 times per day for 21 days	Azithromycin 500 mg on 3 consecutive days each week for 3 consecutive weeks[c]
Non-focal symptoms	Doxycycline 100 mg twice per day or 200 mg once per day for 21 days	Amoxicillin 1 g 3 times per day for 21 days	Azithromycin 500 mg on 3 consecutive days each week for 3 consecutive weeks[c]
Lyme disease affecting the cranial nerves or peripheral nervous system	Doxycycline 100 mg twice per day or 200 mg once per day for 21 days	Amoxicillin 1 g 3 times per day for 21 days	
Lyme disease affecting the central nervous system	Intravenous ceftriaxone 2 g twice per day or 4 g once per day for 21 days (consider switching to oral doxycycline when no longer acutely unwell)	Doxycycline 200 mg twice per day or 400 mg once per day for 21 days	
Arthritis	Doxycycline 100 mg twice per day or 200 mg once per day for 28 days	Amoxicillin 1 g 3 times per day for 28 days	Intravenous ceftriaxone 2 g once per day for 28 days
Acrodermatitis chronica atrophicans	Doxycycline 100 mg twice per day or 200 mg once per day for 28 days	Amoxicillin 1 g 3 times per day for 28 days	Intravenous ceftriaxone 2 g once per day for 28 days
Carditis[b]	Doxycycline 100 mg twice per day or 200 mg once per day for 21 days	Intravenous ceftriaxone 2 g once per day for 21 days	
Carditis and haemodynamically unstable	Intravenous ceftriaxone 2 g once per day for 21 days (consider switching to oral doxycycline when no longer acutely unwell)		

[a] For Lyme disease suspected during pregnancy, use appropriate antibiotics for stage of pregnancy.
[b] Do not use azithromycin to treat adults with cardiac abnormalities associated with Lyme disease because of its effect on QT interval.
[c] At the time of consultation (September 2017), azithromycin did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance,

taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

Table 2: Antibiotic treatment for Lyme disease in children (under 12) according to symptoms[a]

Symptoms	Treatment	Alternative
Erythema migrans	Amoxicillin 30 mg/kg 3 times per day for 21 days up to a maximum of 1 g/dose	Azithromycin 10 mg/kg on 3 consecutive days each week for 3 weeks[b]
Non-focal symptoms	Amoxicillin 30 mg/kg 3 times per day for 21 days up to a maximum of 1 g/dose	Azithromycin 10 mg/kg on 3 consecutive days each week for 3 weeks[b]
Lyme disease affecting the cranial nerves or peripheral nervous system	Amoxicillin 30 mg/kg 3 times per day for 21 days up to a maximum of 1 g/dose	
Lyme disease affecting the central nervous system	Intravenous ceftriaxone 80 mg/kg once per day for 21 days	
Arthritis	Amoxicillin 30 mg/kg 3 times per day for 28 days up to a maximum of 1 g/dose	Intravenous ceftriaxone 80 mg/kg once per day for 28 days
Acrodermatitis chronica atrophicans	Amoxicillin 30 mg/kg 3 times per day for 28 days up to a maximum of 1 g/dose	Intravenous ceftriaxone 80 mg/kg once per day for 28 days
Carditis	Intravenous ceftriaxone 80 mg/kg once per day for 21 days	
Carditis and haemodynamically unstable	Intravenous ceftriaxone 80 mg/kg once per day for 21 days	

[a] Specialist practice may include use of doxycycline for children aged 9 years and above in infections where doxycycline is considered first line in adult practice. At the time of consultation (September 2017), doxycycline did not have a UK marketing authorisation for this indication in children under 12 years and is contraindicated. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[b] At the time of consultation (September 2017), azithromycin did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

To find out why the committee made the recommendations on antibiotic treatment and how they might affect practice, see rationale and impact.

Persistent symptoms after a course of antibiotics

1.3.7 If symptoms that may be related to Lyme disease persist or worsen after antibiotic treatment, review the person's history and examination to explore:

- any possible alternative causes of the symptoms
- if re-infection may have occurred
- details of any previous treatment, including whether the course of antibiotics was completed without interruption
- if symptoms may be related to organ damage caused by Lyme disease, for example, nerve palsy.

1.3.8 If the person's history suggests re-infection, offer antibiotic treatment according to their symptoms (see tables 1 and 2).

1.3.9 Consider a second course of antibiotics for people with persisting symptoms if treatment may have failed. Use an alternative antibiotic to that used for initial treatment, for example for adults with Lyme disease and arthritis, offer amoxicillin if the person has completed an initial course of doxycycline.

1.3.10 Do not routinely offer further antibiotics if a person has persisting symptoms following 2 courses of antibiotics. Consider discussion with or referral to a specialist as outlined in recommendation 1.2.19.

1.3.11 Explain to people with persisting symptoms following antibiotic treatment that:

- symptoms of Lyme disease may take months to resolve even after treatment
- continuing symptoms does not necessarily mean they still have an active infection

- symptoms may be a consequence of damage from infection
- there may be an alternative diagnosis.

1.3.12 Support people who have a slow recovery from Lyme disease by:

- encouraging and helping them to access additional services, including referring to adult social care for a care and support needs assessment, if they would benefit from these
- communicating with social services, educational services and employers about the person's need for gradual return to activities, if relevant.

To find out why the committee made the recommendations on persistent symptoms and how they might affect practice, see rationale and impact.

Non-antibiotic management of symptoms

1.3.13 Assess and offer additional treatment if needed for symptoms of Lyme disease following usual clinical practice (for example, heart block).

1.3.14 Be alert to the possibility of symptoms related to Lyme disease that may need assessment and management, including:

- depression and anxiety (see NICE's guideline on common mental health disorders)
- chronic pain
- sleep disturbance
- fatigue.

To find out why the committee made the recommendations on non-antibiotic management of symptoms and how they might affect practice, see rationale and impact.

Lyme disease during and after pregnancy

1.3.15 Manage suspected Lyme disease during pregnancy in the same way as for people who are not pregnant, but use appropriate antibiotics for stage of pregnancy.

1.3.16 Inform women with Lyme disease during pregnancy that they are unlikely to pass the infection to their baby, and emphasise the importance of completing the full course of antibiotic treatment.

1.3.17 Advise women to tell their healthcare professional that they had Lyme disease during pregnancy if they have concerns about their baby.

1.3.18 For babies born to mothers who had Lyme disease in pregnancy:

- discuss management with a paediatric infectious disease specialist
- treat babies if there is any suspicion that they may be infected or if the baby's serology shows IgM antibodies specific to Lyme disease.

To find out why the committee made the recommendations on Lyme disease during and after pregnancy and how they might affect practice, see rationale and impact.

1.4 Information for people with Lyme disease

1.4.1 Explain to people diagnosed with Lyme disease that:

- Lyme disease is a bacterial infection treated with antibiotics
- most people recover completely
- prompt antibiotic treatment reduces the risk of further symptoms developing and increases the chance of complete recovery
- it may take time to get better, but their symptoms should continue to improve in the months after antibiotic treatment
- they may need additional treatment for symptom relief.

1.4.2 Explain to people who are starting antibiotic treatment for Lyme disease that some people may experience a worsening of symptoms early in

treatment. Tell them to contact their doctor if this happens and not to stop their antibiotic treatment.

1.4.3 Advise people to talk to their doctor if their symptoms have not improved or if symptoms return after completing treatment.

1.4.4 Explain to people with Lyme disease that infection does not give them lifelong immunity and that it is possible for them to be re-infected and develop Lyme disease again.

To find out why the committee made the recommendations on information for people with Lyme disease and how they might affect practice, see rationale and impact.

Recommendations for research

The guideline committee has made the following recommendations for research.

1 Core outcome set for studies of management of Lyme disease

Can a core outcome set be developed for clinical trials of management of Lyme disease?

Why this is important

Antibiotic treatment is the mainstay of management for Lyme disease. The studies published on the management of Lyme disease use differing outcomes, which are often poorly defined. The development of a core outcome set was identified as a high priority because it would allow comparison across trials and allow appropriate meta-analysis to strengthen results. The method used should be patient-focused and include patient input on priority outcomes and should determine core outcomes and how they should be measured.

2 Clinical epidemiology of Lyme disease in the UK

What are the incidence, presenting features, management and outcome of Lyme disease, including in women with Lyme disease who are pregnant, in the UK?

Why this is important

There is a lack of robust epidemiological data on Lyme disease in the UK, particularly in people who are immunocompromised or pregnant. A large clinico-epidemiological study to collect data on incidence, presenting clinical features, management and outcome of Lyme disease in community and hospital settings in the UK would generate population-based statistics. These statistics would enable interventions such as antibiotic treatment and service improvements to be assessed properly, and for services to be tailored so they best serve people with Lyme disease; this was felt to be of high priority. There is no current requirement to notify cases of Lyme disease, therefore, current data are likely to under-estimate the number of people who are seen and treated in the community without serological testing. The morbidity of those who are not rapidly diagnosed and those who seek and receive non-standardised care outside the NHS would justify the costs of this large study.

3 Seroprevalence of Lyme disease-specific antibodies (and other tick-borne infections in the UK population)

What is the current seroprevalence of Lyme disease-specific antibodies and other tick-borne infections (such as babesiosis, ehrlichiosis, anaplasmosis, bartonellosis or Q fever) in people in the UK when performed using UK-accredited assays (ELISA based on C6 antigen and immunoblot)?

Why this is important

This information is not currently available and is of high priority. Without understanding the underlying population seroprevalence of Lyme disease-specific antibodies in the UK, it is impossible to interpret incidence data accurately and to understand fully the epidemiology of Lyme disease in the UK. The available data suggests there are areas of higher and lower prevalence in the UK but with many gaps in knowledge. The information will help to interpret serology of individuals living in endemic areas, where positive serological results may be more common and may not always indicate an acute or recent infection. This will be of benefit to patients and healthcare workers in the UK treating or affected by Lyme disease. Many patients are concerned about the possible presence of co-infections transmitted by ticks: these are thought to be rare in the UK (compared to, for example, the east coast of

US) but we have no data to confirm or refute this. Better evidence may improve diagnostic and treatment decisions.

4 Antimicrobial management of Lyme disease

What are the most clinically and cost-effective treatment options for different clinical presentations of Lyme disease in the UK?

Why this is important

The evidence on the effectiveness of antimicrobial treatment regimens used in different presentations of Lyme diseases is of poor quality, out-dated and often based on small studies. Most studies are not UK based. No relevant cost-effectiveness evidence was identified. A series of prospective multicentre studies is needed to compare the clinical and cost-effectiveness of different dosages and length of treatment, and the clinical and cost-effectiveness of oral compared to intravenous treatments for different presentations of Lyme disease. This is felt to be of high priority as it has enormous implications for patients and for NHS costs. There is currently insufficient quality evidence on the most effective drug and dose, and the effectiveness of extended treatment or retreatment regimens in those with continuing symptoms remains uncertain. Clarification could improve outcomes, reduce costs and may minimise unnecessary treatment.

5 What are the best laboratory tests to diagnose initial and ongoing infection and determine re-infection in the different presentations of Lyme disease in the UK

What is the most clinically and cost effective serological antibody-based test, biomarker (such as CXCL13), lymphocyte transformation and ELISPOT for diagnosing Lyme disease in the UK at all stages, including reinfection?

Why this is important

Determining the most clinically and cost effective diagnostic tests for Lyme disease will improve patient care and is of high priority. The clinical presentation of Lyme disease is very variable, with diagnosis of all presentations except erythema migrans relying in part on laboratory testing. Current literature suggests that a combined IgG/IgM ELISA based on the C6 peptide and immunoblot are useful but published

evidence is of either low or very low quality and is not UK based. There is evidence of variation in the C6 peptide between the principal Borrelia genospecies in UK ticks and a combination of ELISAs may improve sensitivity.

A ‘test of cure’ for Lyme disease does not exist, and, consistent with most other infectious diseases, positive serology is likely to remain positive following successful treatment of acute infection in the majority of patients. However, we know little about the evolution of antibody titres over time in those who have been treated successfully and in those who have persisting symptoms. It is frequently stated that early antibiotic treatment of Lyme disease abrogates the immune response, so that serology remains or becomes negative. The evidence base for this is minimal, and this is not a common occurrence in other infections. Understanding the natural course of Lyme disease serology and non-serological tests over time may assist in the interpretation of test results in patients who remain symptomatic and in those who are high risk for re-infection, such as those with occupational exposure.

In particular, further research into the value of CXCL13 and other biomarkers including, ELISPOT testing and lymphocyte transformation tests may be helpful to support the current low quality evidence.

Rationale and impact

Awareness of Lyme disease

Why the committee made recommendations 1.1.1 to 1.1.3

The committee agreed that raising awareness is of great importance to improve diagnosis and management of Lyme disease. The recommendations highlight how infection occurs, typical tick habitats and areas of higher prevalence, based on evidence of incidence and the committee’s knowledge and experience. This may be helpful to guide healthcare professionals, for example, in recognising the possibility of Lyme disease when a person is unaware that they have been bitten by a tick, or in areas where ticks are found but where Lyme disease is not highly prevalent.

How the recommendations might affect practice

These recommendations aim to improve awareness of Lyme disease, to promote early investigation and treatment, and to optimise outcomes in people with Lyme disease. They will change current practice by prompting healthcare professionals to think about the possibility of Lyme disease. These recommendations are not considered to have a significant resource impact because considering Lyme disease as a differential diagnosis does not necessarily result in any testing for Lyme disease. Furthermore, the number of people with Lyme disease is generally low.

Full details of the evidence and the committee's discussion are in evidence review A: awareness of Lyme disease.

Clinical assessment

Why the committee made recommendations 1.2.1 to 1.2.10

Lyme disease has a varied presentation and is uncommon, so it may sometimes be difficult to identify.

The diagnostic accuracy of key signs and symptoms of Lyme disease (erythema migrans, facial palsy, lymphocytoma, acrodermatitis chronica atrophicans and heart block or arrhythmias) was reviewed to assess if any could be used to diagnose Lyme disease or to indicate that testing should be carried out.

Erythema migrans only occurs in Lyme disease and can be used to diagnose Lyme disease. Some healthcare professionals may not be familiar with erythema migrans, so a description of the rash and its characteristics was included.

Erythema migrans is not always present in Lyme disease, and so the assessment of other signs and symptoms is important. The evidence was not strong enough for the committee to recommend diagnosis, testing or treatment based on any other symptom or sign alone. The committee noted a number of potential presentations of Lyme disease, which should prompt a discussion about the possibility of tick exposure. Factors to consider in history and presentation are highlighted to help with clinical decision-making.

How the recommendations might affect practice

Current practice is to diagnose and treat erythema migrans as Lyme disease. Those who present without erythema migrans, but whose history and presentation is consistent with Lyme disease, receive diagnostic testing. The recommendations will not change current practice but may serve as a reminder to healthcare professionals to think about Lyme disease as a differential diagnosis, particularly in areas where Lyme disease is less common. As a result, the committee did not consider that these recommendations would have a resource impact.

Full details of the evidence and the committee's discussion are in evidence review B: diagnostic accuracy of signs and symptoms.

Laboratory investigations

Why the committee made recommendations 1.2.11 to 1.2.22

Many symptoms associated with Lyme disease have more common causes, so testing is helpful to ensure accurate diagnosis and appropriate treatment.

The majority of Lyme disease tests rely on examination of blood for presence of antibodies and need careful interpretation alongside clinical assessment.

There is uncertainty over which test or combination of tests are most helpful in diagnosing Lyme disease. The committee agreed that initial testing with a combination IgM and IgG ELISA for Lyme disease should be offered because the evidence generally showed better accuracy (both sensitivity and specificity) for combined tests compared to IgM-only and IgG-only tests. There was evidence that tests based on the C6 synthetic peptide or validated sets of purified antigens have a relatively high degree of sensitivity for detecting people with Lyme disease so this was also specified in the recommendation to provide greater accuracy and consistency across results.

If the initial ELISA test is positive or equivocal, the committee agreed that an immunoblot test should be offered to confirm diagnosis. The evidence suggested that the combination of initial IgM and IgG ELISA and confirmatory IgM and IgG immunoblot testing had a high sensitivity and specificity, particularly for Lyme arthritis, Lyme carditis and acrodermatitis chronica atrophicans.

For people with a negative ELISA result who continue to have symptoms clinical review is recommended to ensure that alternative diagnoses are not missed. Since antibodies take some time to develop repeat testing is recommended for people who may have had the initial test too early, before an immune response has developed. If symptoms have been present for 12 weeks, the committee agreed that the ELISA may be repeated and an immunoblot should be carried out, which will help rule out or confirm diagnosis where uncertainty still remains.

Because of the limitations of tests for Lyme disease the committee also agreed that people with negative test results who continue to have symptoms might be discussed with or referred to an infectious disease specialist or a specialist appropriate for the person's symptoms to review whether further tests are needed or to consider alternative diagnoses.

Diagnostic tests should be validated before they are used to diagnose Lyme disease as otherwise tests may yield unreliable and misleading results, which may lead to misdiagnosis. The committee agreed that testing should be done in NHS-accredited laboratories.

The committee agreed that *Borrelia* infection does not behave differently in children than adults, but acknowledged that a young child's immune responses might not be as rapid and effective. The limited evidence in children did not show a noticeable difference in test accuracy compared to adults.

How the recommendations might affect practice

A 2-tier testing system is used in current practice, in which a positive result on an initial ELISA leads to a confirmatory immunoblot test. A negative result on an initial ELISA would not usually lead to a confirmatory immunoblot test. Therefore, the recommendation to repeat the ELISA and carry out an immunoblot test, despite an initial negative ELISA, when there is clinical suspicion of Lyme disease would be a change to practice and increase the number of people receiving these tests. However, this would only apply to a small population, so this recommendation is not likely to have a significant resource impact.

Full details of the evidence and the committee's discussion are in evidence review C: diagnostic tests.

Emergency referral and referral for children and young people

Why the committee made recommendations 1.3.1 and 1.3.2

Lyme disease will not usually be considered as the most likely cause when people present with neurological and other symptoms that need emergency referral (such as central nervous system infection or heart block). However, the committee wanted to emphasise that if the history and physical findings suggest Lyme disease, usual clinical practice is still appropriate, as people may need additional supportive treatment from specialist services as well as appropriate antibiotics.

The type of problems that children with Lyme disease may develop, such as facial palsy, are uncommon and the committee decided to recommend that children and young people with these presentations should be discussed with a specialist to ensure the diagnosis is correct and for advice on antibiotic treatment.

How the recommendations might affect practice

People who are systemically unwell with neurological or cardiac disease are referred to hospital for urgent treatment, so this recommendation should not lead to a change in existing practice.

The occurrence of symptoms such as arthritis and facial palsy are uncommon in children, so it is expected that most children with these symptoms are already seen in specialist services; therefore, this recommendation should not result in a large change of practice.

Full details of the evidence and the committee's discussion are in evidence review D: management of erythema migrans.

Antibiotic treatment

Why the committee made recommendations 1.3.3 and 1.3.4

The committee considered it important to standardise dose and duration of treatments for people with Lyme disease across different presentations to ensure consistency and clarity for treatment.

Erythema migrans

A number of studies examined antibiotic treatment of Lyme disease with erythema migrans using different antibiotics, doses and durations of treatment. The evidence was all of poor quality.

For adults, there was evidence that doxycycline is more clinically effective than some other antibiotics. However, the evidence showed no clear difference in effectiveness between doxycycline, an amoxicillin/probenecid combination and azithromycin. It was noted that doxycycline and amoxicillin are able to penetrate the blood–cerebrospinal fluid barrier and pass into the central nervous system, whereas azithromycin cannot. This may be important to prevent the development of further symptoms. Doxycycline can also be taken in a single daily dose, which may help with adherence. Considering these factors, the committee agreed to recommend doxycycline as an initial treatment for adults and young people (aged over 12), with amoxicillin as an alternative, and azithromycin as a third option when both doxycycline and amoxicillin are contraindicated. There was no benefit of intravenous or intramuscular cephalosporin over doxycycline.

For children there was evidence that amoxicillin and azithromycin were equally effective. The committee agreed that children under 12 should be offered amoxicillin as an initial treatment, with azithromycin recommended as an alternative treatment option and that doses should be adjusted by weight.

Current practice is for a course of 14 or 21 days of an antibiotic. There was some evidence of a greater reduction in symptoms using a longer course of doxycycline and that there were no additional adverse events when compared with a shorter course. Some studies also showed more treatment failure and ongoing symptoms with shorter courses. Therefore, the committee agreed on a 21-day antibiotic course for adults, young people and children.

Full details of the evidence and the committee's discussion are in evidence review D: management of erythema migrans.

Non-focal symptoms of Lyme disease

People diagnosed with Lyme disease often have symptoms that are not specific to an organ system (such as fever, sweats, muscle pain), which are referred to here as 'non-focal' symptoms.

No studies were identified comparing different antibiotics for management of Lyme disease in people with non-focal symptoms. However, the committee reviewed the evidence available for treating other symptoms and agreed that people with non-focal symptoms should be given the same treatment as people with erythema migrans.

Full details of the evidence and the committee's discussion are in evidence review E: management of non-specific symptoms.

Lyme disease affecting the cranial nerves, peripheral nervous system or central nervous system

Lyme disease can affect the nervous system and cause a number of different problems including meningitis, encephalitis, cranial nerve palsies and radiculopathies.

A study comparing oral doxycycline with intravenous ceftriaxone showed a greater benefit with oral doxycycline. However, both treatments showed low rates of cure (full resolution of neurological symptoms). The committee noted that the study used a short, 14-day course of antibiotics and felt that a longer course could be beneficial.

The committee considered that people presenting with meningitis or encephalitis (prior to a diagnosis of Lyme disease) would receive treatment with intravenous ceftriaxone, and that intravenous treatment would achieve adequate concentrations in the central nervous system more rapidly than oral treatment.

The committee discussed the management of neurosyphilis, which has similar central nervous system involvement. The committee considered that, although the evidence was limited, central nervous system symptoms in Lyme disease should be treated with a similar antibiotic dose to that recommended for neurosyphilis.

Once-daily ceftriaxone has the advantage of being given more easily as an outpatient treatment than other intravenous options, which allows completion of the course as an outpatient.

Taking these factors into account, the committee agreed that a 21-day course of intravenous ceftriaxone 4 g daily was recommended as initial treatment for adults and young people (aged 12 and over) with Lyme disease affecting the central nervous system, with a 21-day course of doxycycline 400 mg daily recommended as an alternative treatment. A 21-day course of doxycycline 200 mg daily should be offered as initial treatment for adults and young people (aged 12 and over) with Lyme disease affecting the cranial nerves or the peripheral nervous system, with a 21-day course of amoxicillin recommended as an alternative treatment.

No studies were identified for nervous system symptoms in children. The guideline recommends that care of children and young people less than 18 years should be discussed with a specialist for advice about diagnosis and management and provides recommendations for children under 12 based on those for adults, with the same duration of treatment but using appropriate antibiotics for children and doses adjusted by weight.

Full details of the evidence and the committee's discussion are in evidence review F: management of neuroborreliosis.

Arthritis

Lyme disease can cause inflammation affecting one or more joints.

The studies identified looked at antibiotic treatment in children, young people and adults. One study found that a 30-day course of doxycycline resulted in fewer symptom relapses and adverse events than 30 days of amoxicillin plus probenecid.

The committee agreed that longer courses of treatment are appropriate when treating arthritis associated with Lyme disease because it is difficult for antibiotics to penetrate to the synovium and synovial fluid.

Taking these factors into account, the committee decided that a 28-day course of doxycycline 200 mg daily should be offered to adults and young people (aged 12 and

over) as initial treatment, with a 28-day course of amoxicillin recommended as an alternative treatment. A 28-day course was recommended, as the committee was aware that antibiotics are available in weekly packs. The committee also agreed that if oral doxycycline and amoxicillin are contraindicated or unsuitable, 28 days of intravenous ceftriaxone should be offered.

The committee agreed that the evidence supported similar treatment to adults for children under 12, with the same duration of treatment but using appropriate antibiotics for children and doses adjusted by weight.

Full details of the evidence and the committee's discussion are in evidence review G: management of arthritis.

Acrodermatitis chronica atrophicans

Acrodermatitis chronica atrophicans is a rare manifestation of Lyme disease; a progressive skin rash that may present months to years after initial infection.

The studies identified indicated that 30-day course of doxycycline was better for treating acrodermatitis chronica atrophicans than a 20-day course of treatment. Oral doxycycline was also better than intravenous ceftriaxone daily when both were given for 30 days. The committee agreed that the longer course of treatment might be appropriate because it is difficult for antibiotics to penetrate the affected skin. A 28-day course was recommended because the committee was aware that antibiotics are available in weekly packs.

Considering these factors, the committee decided that a 28-day course of doxycycline should be offered to adults and young people (aged 12 and over) as the initial treatment, with a 28-day course of amoxicillin recommended as an alternative treatment. The committee also agreed that if oral doxycycline and amoxicillin are contraindicated or unsuitable, intravenous ceftriaxone could be offered.

There was no evidence found for treatment of acrodermatitis chronica atrophicans in children.

The guideline recommends that care of children and young people under 18 should be discussed with a specialist for advice about diagnosis and management.

Full details of the evidence and the committee's discussion are in evidence review H: management of acrodermatitis chronica atrophicans.

Carditis

Lyme disease may rarely affect the heart, causing inflammation (carditis) that can result in heart block or other heart problems.

No studies of antibiotic treatment for heart problems caused by Lyme disease were identified. Therefore, the committee reviewed the evidence available for treating other symptoms of Lyme disease and used their knowledge of care for people with heart problems. The committee considered it important to standardise dose and duration of treatments for people with Lyme disease to ensure consistency and clarity for treatment.

The committee decided that a 21-day course of doxycycline 200 mg daily should be offered as initial treatment to adults and young people (aged 12 and over) with carditis who are stable, with a 21-day course of intravenous ceftriaxone recommended as an alternative treatment.

The committee also noted that people with severe heart problems are likely to need treatment in hospital from cardiologists. They agreed that intravenous ceftriaxone for 21 days should be offered as initial treatment for people with carditis who are haemodynamically unstable.

The committee decided that treatment for children under 12 should be based on that for adults, with the same duration of treatment but using appropriate antibiotics for children and doses adjusted by weight. The guideline includes a recommendation that children and young people under 18 should have their care discussed with a specialist.

It was noted that azithromycin should not be used to treat people with cardiac abnormalities associated with Lyme disease because of its effect on the QT interval.

Full details of the evidence and the committee's discussion are in evidence review I: management of carditis.

Lymphocytoma and ocular symptoms

Lymphocytoma is a rare early presentation of Lyme disease. The guideline committee agreed not to make a recommendation for the antibiotic management of lymphocytoma because no evidence was identified, and the committee agreed that a person presenting with lymphocytoma only was likely to require specialist investigation of lesions to establish the diagnosis in most cases. For people with a clear supportive history and other symptoms suggesting Lyme disease as the likely diagnosis, the committee agreed that they would receive treatment appropriate for their other symptoms.

Full details of the evidence and the committee's discussion are in evidence review J: management of lymphocytoma.

The guideline committee did not make any recommendations because no evidence for the management of non-neurological ocular manifestations of Lyme disease was identified. The committee decided that specialist investigation was likely unless there was clear support from history and other symptoms that Lyme disease was the likely diagnosis.

Full details of the evidence and the committee's discussion are in evidence review K: management of ocular symptoms.

How the recommendations might affect practice

The recommendations aim to standardise antibiotic treatment, providing a consistent framework for good practice in managing Lyme disease. Overall, there may be changes to prescribing practices, but the impact is likely to be small.

Full details of the evidence and the committee's discussion are in the evidence reviews.

Persistent symptoms after a course of antibiotics and non-antibiotic management of symptoms

Why the committee made recommendations 1.3.7 to 1.3.14

People who have had treatment for Lyme disease sometimes report persisting symptoms. These may be caused by re-infection, insufficient initial treatment or lack

of adherence to treatment, or organ damage caused by Lyme disease, which may take a long time to heal or may even be permanent.

The evidence available did not show benefit from prolonged treatment with antibiotics, but the committee agreed that treatment failure could occur and that a second course of antibiotics might sometimes be appropriate. The committee noted the importance of considering alternative diagnoses to prevent inappropriate antibiotic treatment and misdiagnosis.

The committee recommended that people with persisting symptoms should not routinely be offered more than 2 courses of antibiotics because of lack of evidence of benefit. However, discussion with a specialist or referral should be considered in some cases.

People who have a slow recovery from Lyme disease may need additional support and access to social services. The committee felt that it was important to recommend that healthcare professionals help people with long-term symptoms related to Lyme disease to access support if needed.

No specific evidence review was carried out to inform recommendations on support, referral to social services or the need to consider assessing and managing other symptoms related to Lyme disease, such as chronic pain, fatigue or depression. The committee, however, acknowledged that some people with Lyme disease experience a slow recovery and may require professional support. Some people with Lyme disease feel that their needs are not considered in an appropriate way and the committee therefore decided to recommend that physicians consider the possibility of such needs.

How the recommendations might affect practice

Current treatment for Lyme disease is a single course of antibiotics. Treatment for persisting symptoms is unclear and practice varies. Further antibiotic treatment is now recommended as an option if persisting infection is a possibility. This will standardise practice but may cause an increase in antibiotic prescribing in a small number of patients. The committee agreed that this change in practice would not result in a significant resource impact given the small number of people with recurrent symptoms.

Some people with Lyme disease may require support or social services, especially when they have a slow recovery. Social services needs assessments are carried out by local authorities and will not affect NHS practice.

Some people with Lyme disease may also present with related symptoms, such as chronic pain, depression or fatigue. Guidance for managing these symptoms already exists and therefore there will be no change to existing clinical practice.

Full details of the evidence and the committee's discussion are in evidence review L: management of persistent symptoms.

Lyme disease during and after pregnancy

Why the committee made recommendations 1.3.15 to 1.3.18

The committee acknowledged that mother-to-baby transmission of Lyme disease is possible in theory. There was an absence of evidence, but the risk appears to be very low. The committee decided that women could be reassured that pregnancy and their baby are unlikely to be affected, and highlighted the importance of completing treatment. It was also agreed that pregnant women should be treated following usual practice, but using antibiotics suitable in pregnancy.

There is no standard approach to caring for babies born to mothers with Lyme disease, and symptoms of Lyme disease in babies are not known. Therefore, the committee agreed that recommendations about treatment and follow-up for babies would be helpful.

Given the absence of evidence, the committee agreed that care of babies born to mothers with Lyme disease should be discussed with a paediatric infectious disease specialist. In addition, to ensure that babies with Lyme disease do not go untreated, treatment is recommended for babies with serology showing IgM antibodies specific to Lyme disease or if there is clinical suspicion that a baby has symptoms that might be caused by Lyme disease.

How the recommendations might affect practice

There is no standardised approach to diagnosis and management of Lyme disease in babies born to a mother with Lyme disease. The recommendations are unlikely to

have a considerable impact on practice but provide guidance to reassure women and healthcare professionals.

Full details of the evidence and the committee's discussion are in evidence review M: person-to-person transmission.

Information about tests and information for people with Lyme disease

Why the committee made recommendations 1.2.23 to 1.2.26 and 1.4.1 to 1.4.4

There was a lack of evidence identified on the information needs of people with suspected or confirmed Lyme disease, or specific Lyme disease presentations. However, some evidence was identified that highlighted the need for information addressing medical uncertainty. The guideline committee used this evidence, the evidence reviews on diagnosis and management, and their experience to make recommendations to inform people being investigated for and diagnosed with Lyme disease. The committee agreed that people would benefit from a better understanding of the nature of Lyme disease, the accuracy and limitations of testing, and issues with treatment and follow-up.

How the recommendations might affect practice

The recommendations standardise and reinforce good practice, and many healthcare professionals will not need to change their current practice.

Full details of the evidence and the committee's discussion are in evidence review N: information needs.

Putting this guideline into practice

[This section will be completed after consultation]

NICE has produced tools and resources to help you put this guideline into practice.

Putting recommendations into practice can take time. How long may vary from guideline to guideline, and depends on how much change in practice or services is needed. Implementing change is most effective when aligned with local priorities.

Changes recommended for clinical practice that can be done quickly – like changes in prescribing practice – should be shared quickly. This is because healthcare professionals should use guidelines to guide their work – as is required by professional regulating bodies such as the General Medical and Nursing and Midwifery Councils.

Changes should be implemented as soon as possible, unless there is a good reason for not doing so (for example, if it would be better value for money if a package of recommendations were all implemented at once).

Different organisations may need different approaches to implementation, depending on their size and function. Sometimes individual practitioners may be able to respond to recommendations to improve their practice more quickly than large organisations.

Here are some pointers to help organisations put NICE guidelines into practice:

1. **Raise awareness** through routine communication channels, such as email or newsletters, regular meetings, internal staff briefings and other communications with all relevant partner organisations. Identify things staff can include in their own practice straight away.

2. **Identify a lead** with an interest in the topic to champion the guideline and motivate others to support its use and make service changes, and to find out any significant issues locally.

3. **Carry out a baseline assessment** against the recommendations to find out whether there are gaps in current service provision.

4. **Think about what data you need to measure improvement** and plan how you will collect it. You may want to work with other health and social care organisations and specialist groups to compare current practice with the recommendations. This may also help identify local issues that will slow or prevent implementation.

5. **Develop an action plan**, with the steps needed to put the guideline into practice, and make sure it is ready as soon as possible. Big, complex changes may take longer to implement, but some may be quick and easy to do. An action plan will help in both cases.

6. **For very big changes** include milestones and a business case, which will set out additional costs, savings and possible areas for disinvestment. A small project group could develop the action plan. The group might include the guideline champion, a senior organisational sponsor, staff involved in the associated services, finance and information professionals.

7. **Implement the action plan** with oversight from the lead and the project group. Big projects may also need project management support.

8. **Review and monitor** how well the guideline is being implemented through the project group. Share progress with those involved in making improvements, as well as relevant boards and local partners.

NICE provides a comprehensive programme of support and resources to maximise uptake and use of evidence and guidance. See our into practice pages for more information.

Also, see Leng G, Moore V, Abraham S, editors (2014) Achieving high quality care – practical experience from NICE. Chichester: Wiley.

Context

Lyme disease (Lyme borreliosis) is a tick-borne infectious disease. It is caused by a specific group of *Borrelia burgdorferi* bacteria, which can be transmitted to humans through a bite from an infected tick. Infection is more likely the longer a tick is attached to the skin. Ticks live in areas of overgrown vegetation, both in rural and urban areas. People who spend time in these areas for work or recreation are at increased risk of tick exposure.

Lyme disease can occur anywhere in the UK, although some areas have a higher reported incidence. Approximately 50% of laboratory-confirmed cases are diagnosed in the South East and South West of England. High incidence is also reported in Scotland. Worldwide, Lyme disease occurs mainly in the northern hemisphere, and travellers to specific areas of Europe, North America and elsewhere may be at risk. However, the true incidence of Lyme disease is unknown.

Public Health England reports that there are approximately 1,000 serologically confirmed cases of Lyme disease each year in England and Wales. Many diagnoses will also be made clinically without laboratory testing. Public Health England estimates between 1,000 and 2,000 additional cases of Lyme disease are diagnosed every year but the true number is unknown.

In England and Wales, cases of laboratory-confirmed Lyme disease have increased. It is not certain how much of the rise is due to increased awareness and how much to the spread of the disease.

Infection with *Borrelia burgdorferi* can go unnoticed. When symptoms occur this is called Lyme disease. Many people may not notice or remember a tick bite. A bite can be followed by an 'erythema migrans' rash, which is sometimes mistaken for cellulitis or ringworm and effective treatment delayed. In the absence of this rash, diagnosis can be difficult because symptoms may be caused by many other conditions as well as Lyme disease.

The terminology around Lyme disease is varied and many poorly defined terms are used in the literature (such as acute Lyme disease, late Lyme disease, chronic Lyme disease and post-Lyme disease). This guideline has avoided using controversial definitions and has concentrated on providing evidence-based advice on diagnosis and treatment, according to the clinical context, presentation, symptoms and available treatments.

The guideline aims to raise awareness of when Lyme disease should be suspected and to ensure that people with suspected Lyme are given early and consistent treatment. The guideline committee have also developed a series of research recommendations to improve basic epidemiology and understanding of the natural history of Lyme disease.

More information

To find out what NICE has said on topics related to this guideline, see our web page on infections.

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