NICE National Institute for Health and Care Excellence

NICE Pathways

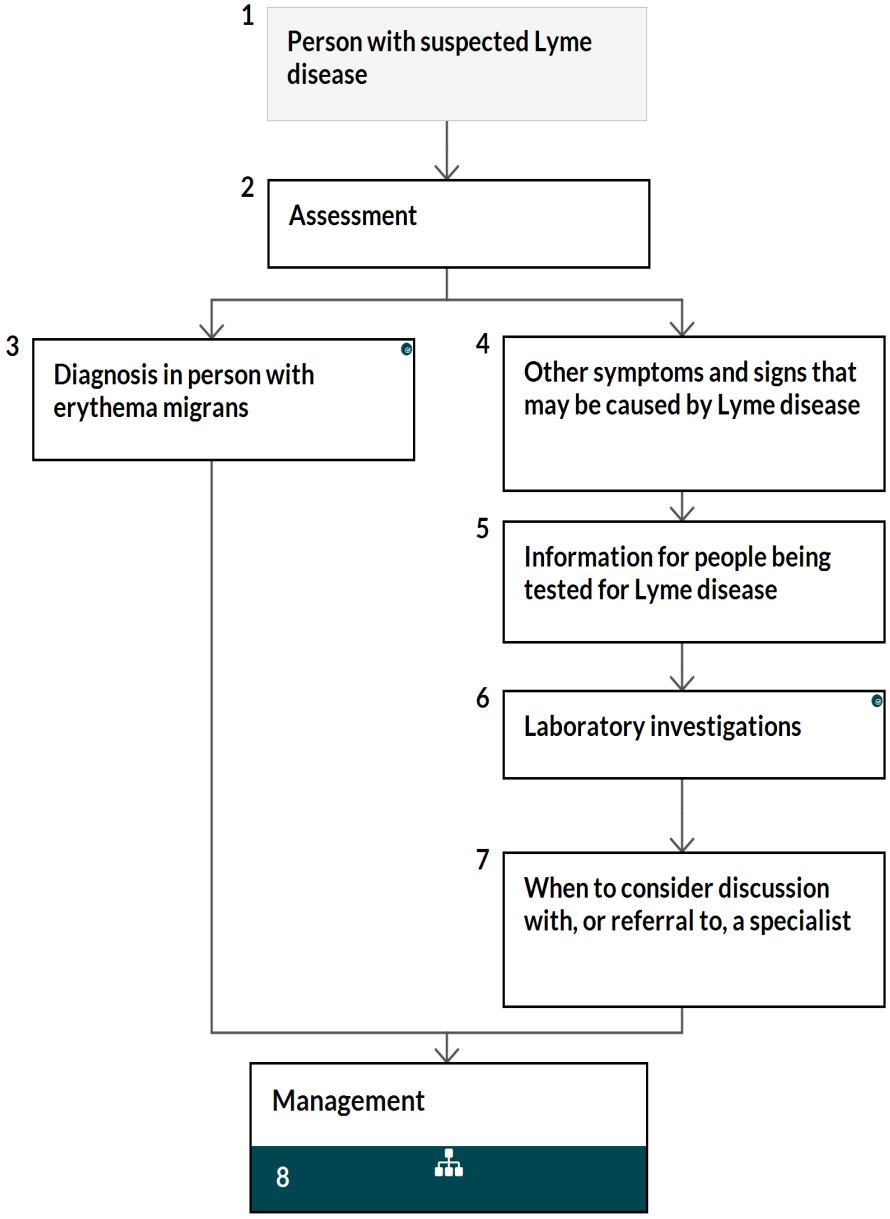
Diagnosing Lyme disease

NICE Pathways bring together everything NICE says on a topic in an interactive flowchart. NICE Pathways are interactive and designed to be used online.

They are updated regularly as new NICE guidance is published. To view the latest version of this NICE Pathway see:

http://pathways.nice.org.uk/pathways/lyme-disease
NICE Pathway last updated: 09 July 2019

This document contains a single flowchart and uses numbering to link the boxes to the associated recommendations.



1 Person with suspected Lyme disease

No additional information

2 Assessment

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 highly prevalent.

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

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

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

- missing an alternative diagnosis
- providing inappropriate treatment.

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

Take into account that people with Lyme disease may have symptoms of cognitive impairment and may have difficulty explaining their symptoms. For adults, follow NICE's recommendations on patient experience in adult NHS services.

Why we made the recommendations

See information on clinical assessment [See page 9].

3 Diagnosis in person with erythema migrans

Diagnose Lyme disease in people with erythema migrans, a red rash that:

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

NICE has also produced a resource with images showing erythema migrans.

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

- usually develops and recedes during 48 hours from the time of the tick bite
- is more likely than erythema migrans to be hot, itchy or painful
- may be caused by an inflammatory reaction or infection with a common skin pathogen.

See why we made the recommendations on clinical assessment [See page 9].

Laboratory investigations

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

See why we made the recommendations on laboratory investigations [See page 10].

Quality standards

The following quality statement is relevant to this part of the interactive flowchart.

1. Erythema migrans

4 Other symptoms and signs that may be caused by Lyme disease

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:

- fever and sweats
- swollen glands
- malaise
- fatigue
- neck pain or stiffness

- migratory joint or muscle aches and pain
- cognitive impairment, such as memory problems and difficulty concentrating (sometimes described as 'brain fog')
- headache
- paraesthesia.

Consider the possibility of Lyme disease in people presenting with symptoms and signs relating to 1 or more organ systems (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
- inflammatory arthritis affecting 1 or more joints that may be fluctuating and migratory
- cardiac problems, such as heart block or pericarditis
- eye symptoms, such as uveitis or keratitis
- skin rashes such as acrodermatitis chronica atrophicans or lymphocytoma.

See why we made the recommendations on clinical assessment [See page 9].

Children and young people without erythema migrans

Discuss the diagnosis and management of Lyme disease in children and young people under 18 years with a specialist, unless they have a single erythema migrans lesion and no other symptoms. Choose a specialist appropriate for the child or young person's symptoms dependent on availability, for example, a paediatrician, paediatric infectious disease specialist or a paediatric neurologist.

See why we made the recommendation on specialist advice on diagnosing and managing Lyme disease in children and young people.

5 Information for people being tested for Lyme disease

Tell people that tests for Lyme disease have limitations. Explain that both false-positive and false-negative results can occur and what this means.

Explain to people that most tests for Lyme disease assess for the presence of antibodies, and that the accuracy of tests may be reduced if:

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

Advise people that tests from non-UKAS laboratories may not have been fully evaluated to diagnose Lyme disease.

Explain to people that:

- the symptoms and signs associated with Lyme disease overlap with those of other conditions
- they will be assessed for alternative diagnoses if their tests are negative and their symptoms have not resolved
- symptoms such as tiredness, headache and muscle pain are common and a specific medical cause is often not found.

Why we made the recommendations

See information for people with Lyme disease [See page 10].

6 Laboratory investigations

Use a combination of clinical presentation and laboratory testing to guide diagnosis and treatment in people without erythema migrans. Do not rule out diagnosis if tests are negative but there is high clinical suspicion of Lyme disease.

If there is a clinical suspicion of Lyme disease in people without erythema migrans:

- offer an ELISA test for Lyme disease [See page 9] **and**
- consider starting treatment with antibiotics while waiting for the results if there is a high clinical suspicion.

Test for both IgM and IgG antibodies using ELISAs based on purified or recombinant antigens derived from the VlsE protein or its IR6 domain peptide (such as C6 ELISA).

If the ELISA is positive or equivocal:

- perform an immunoblot test for Lyme disease **and**
- consider starting treatment with antibiotics while waiting for the results if there is a high clinical suspicion of Lyme disease.

If the ELISA for Lyme disease is negative and the person still has symptoms, review their history and symptoms, and think about the possibility of an alternative diagnosis.

If Lyme disease is still suspected in people with a negative ELISA who were tested within 4 weeks from symptom onset, repeat the ELISA 4 to 6 weeks after the first ELISA test.

If Lyme disease is still suspected in people with a negative ELISA who have had symptoms for 12 weeks or more, perform an immunoblot test.

Diagnose Lyme disease in people with symptoms of Lyme disease and a positive immunoblot test.

If the immunoblot test for Lyme disease is negative and symptoms have resolved, explain to the person that no treatment is required.

NICE has produced a visual summary on Lyme disease: laboratory investigations and diagnosis.

UKAS-accredited laboratories

Carry out tests for Lyme disease only at laboratories that:

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

Do not routinely diagnose Lyme disease based only on tests done outside the NHS, unless the laboratory used is accredited, participates in formal external quality assurance programmes and uses validated tests. If there is any doubt about tests:

- review the person's clinical presentation **and**
- carry out testing again using a UKAS-accredited laboratory and/or seek advice from a national reference laboratory.

Why we made the recommendations

See information on laboratory investigations [See page 10].

Quality standards

The following quality statement is relevant to this part of the interactive flowchart.

2. Repeat ELISA tests

7 When to consider discussion with, or referral to, a specialist

If an adult with Lyme disease has focal symptoms, consider a discussion with or referral to a specialist, without delaying treatment. Choose a specialist appropriate for the person's symptoms, for example, an adult infection specialist, rheumatologist or neurologist.

See why we made the recommendation on specialist advice on diagnosing and managing Lyme disease in adults [See page 10].

If the immunoblot test for Lyme disease is negative (regardless of the ELISA result) but symptoms persist, consider a discussion with or referral to a specialist, 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 (both infectious, including other tick-borne diseases, and non-infectious).

Choose a specialist appropriate for the person's history or symptoms, for example, an adult or paediatric infection specialist, rheumatologist or neurologist.

See why we made the recommendations on laboratory investigations [See page 10].

8 Management

See Lyme disease / Managing Lyme disease

Test for Lyme disease

Lyme disease is caused by infection with bacteria from different species of *Borrelia*. The majority of tests for Lyme disease detect antibodies produced in response to infection by bacteria. The term Lyme disease is used when referring to both the disease and to tests for an antibody response. This reflects the terminology used in clinical practice.

Clinical assessment

The committee reviewed evidence on the diagnostic accuracy of some specific signs and symptoms (erythema migrans, facial palsy, lymphocytoma, acrodermatitis chronica atrophicans and heart block or arrhythmias) 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 may be used to diagnose Lyme disease. The committee agreed that the evidence, although limited, supported this. Some healthcare professionals may not be familiar with erythema migrans, so a description of the rash and its characteristics was included.

Lyme disease has a varied presentation and erythema migrans is not always present, 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. However, the committee noted a number of potential presentations of Lyme disease that should alert healthcare professionals to consider the possibility of Lyme disease and prompt a discussion about the possibility of tick exposure. Based on their knowledge and experience, the committee agreed to highlight factors to consider in history and presentation to help with clinical decision-making.

How the recommendations might affect practice

Current practice is to diagnose and treat Lyme disease in people with erythema migrans. People who present without erythema migrans but whose history and presentation are consistent with Lyme disease are offered testing. The recommendations will not change current practice but should serve as a reminder to healthcare professionals, particularly in areas where Lyme disease is less common, to think about Lyme disease as a differential diagnosis. Implementing these recommendations is unlikely to involve additional costs and may improve recognition and diagnosis.

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

Specialist advice on diagnosing and managing Lyme disease in adults

For adults with focal symptoms such as arthritis, the committee agreed that a discussion with a specialist may be considered but that treatment can be started.

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

Information for people with Lyme disease

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 the medical uncertainties of Lyme disease.

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 current good practice. 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.

Laboratory investigations

The committee agreed that laboratory testing is unnecessary for people presenting with erythema migrans, because the rash is very specific to Lyme disease and prompt treatment will prevent further symptoms developing. However, most other symptoms associated with Lyme disease have other more common causes, so testing may be helpful to ensure accurate diagnosis and appropriate treatment.

Based on the evidence on test accuracy, the committee agreed that test results need careful interpretation alongside clinical assessment to guide diagnosis. Because of the limitations of tests, Lyme disease should not be ruled out by negative tests if it is strongly suggested by the clinical assessment. The committee decided that treatment could be started at the same time as testing if clinical assessment strongly suggests Lyme disease because prompt treatment is important.

The committee agreed a strategy of 2-tier testing (an initial and confirmatory test), which the evidence indicated was potentially cost saving. 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. The evidence was best for tests based on purified or recombinant antigens derived from the VlsE protein or its IR6 domain peptide (such as a C6).

For people with a negative ELISA result who continue to have symptoms, the committee agreed that clinical review would ensure that alternative diagnoses are not missed. In addition, because antibodies take some time to develop, repeat testing would be warranted 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 an immunoblot would help rule out or confirm diagnosis where uncertainty still remains.

The committee agreed that for people with negative test results who continue to have symptoms, discussion with or referral to a specialist for further review might beneficial.

The committee agreed that testing should be done in UKAS-accredited laboratories and that any tests used for diagnosis should be validated before they are used to diagnose Lyme disease to avoid unreliable and misleading results, which may lead to misdiagnosis.

Based on their knowledge and experience, the committee agreed that *Borrelia burgdorferi sensu lato (sl)* 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 with adults. Therefore, the committee decided that separate recommendations for testing in children were unnecessary.

The committee considered it important that people being tested for Lyme disease understand how the tests work, their limitations and the importance of basing decisions on tests that are valid.

How the recommendations might affect practice

A 2-tiered 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 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 this test. 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.

Glossary

ELISA

enzyme-linked immunosorbent assay

UKAS

UK accreditation service

Sources

Lyme disease (2018) NICE guideline NG95

Your responsibility

Guidelines

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility

to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

Local commissioners and providers of healthcare have a responsibility to enable the guideline to be applied when individual professionals and people using services wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with complying with those duties.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Technology appraisals

The recommendations in this interactive flowchart represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take these recommendations fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this interactive flowchart is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Commissioners and/or providers have a responsibility to provide the funding required to enable the recommendations to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Medical technologies guidance, diagnostics guidance and interventional procedures

guidance

The recommendations in this interactive flowchart represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, healthcare professionals are expected to take these recommendations fully into account. However, the interactive flowchart does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Commissioners and/or providers have a responsibility to implement the recommendations, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations. Nothing in this interactive flowchart should be interpreted in a way that would be inconsistent with compliance with those duties.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.