PE1662/O
Petitioner submission of 10 February 2020

This submission was first provided in September 2018. This is an updated version

Petitioner objections to NICE Guidelines on Lyme disease

The NICE committee has formally recognised the uncertainties about diagnosing and treating Lyme disease. However, they have not made it sufficiently clear that the evidence underpinning the recommendations is recognised by NICE to be of poor quality or even missing, and they have not allowed chronically ill patients to receive ongoing treatment.

1. Too narrow a scope

The NICE guidelines have too narrow a scope and specifically do not cover "other tick-borne infections". They therefore do not take into account complexities caused by being infected by multiple tick-borne (or other vector-borne) organisms.

There is no consideration of the range of infections which can arise from a tick-bite. Patients in Scotland are testing positive in private tests for a variety of species of co-infections such as Babesia, Bartonella, Anaplasma, Ehlichia, Rickettsia as well as Borrelia. Babesia has been found in 59.6% of badgers in Scotland [1.1] and yet patients find it difficult to access tests. Anaplasma has been found in 73% of sheep, Babesia venatorum in 9% of sheep, and a Babesia odocoilei parasite in 15% of wild deer [1.2], Bartonella has been found in at least 15% of cats [1.3], Q-fever in 1% of cattle [1.4] and yet there are no ISO accredited human tests at the Scottish Lyme and Tick-borne Diseases Reference Laboratory for any co-infections [1.5]. Opportunistic infections such as mycoplasma pneumoniae, chlamydia pneumoniae, viruses, and other organisms are also common in Lyme disease patients. Within NHS Scotland, many of these tests are also hard to access.

There is also no recognition that those infected with both borrelia and co-infections have more complex and more severe illness of longer duration than simple infection with borrelia alone. A French study has shown that of infected ticks, 45% were co-infected, some with up to 5 pathogens [1.6], showing that polymicrobial infections are the rule not the exception. A survey run by Caudwell LymeCo indicated that 94% of UK patients with Lyme disease believed they had at least one co-infection, so it is not rare to be multiply infected. Co-infection with other tick-borne pathogens, particulary Babesia, has been found to increase the length and severity of illness [1.7]. There is nothing in the guidelines to indicate how frequently patients are infected by multiple infections and how it affects treatment.

What patients need is a route to get full diagnosis and treatment from infection caused by a tick-bite, whatever its cause, and whether infected by a single organism or multiple organisms. Guidelines with the narrow scope of only Lyme disease result in

patients being abandoned if they do not have Lyme disease, even if they have other tick-borne infections.

Unlike NICE and other guidelines, the French Protocol for Diagnosis and Care for tick-borne diseases (TBDs) explicitly recommends testing for and treatment of co-infections [1.8].

[1.1] https://www.ncbi.nlm.nih.gov/pubmed/28696186
[1.2] http://theses.gla.ac.uk/8750/
[1.3] https://www.ncbi.nlm.nih.gov/pubmed/21570883
[1.4] https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(70)92829-1/fulltext
[1.5] https://www.ukas.com/wp-content/uploads/schedule_uploads/00007/9612%20Medical%20Single.pdf
[1.6] https://www.ncbi.nlm.nih.gov/pubmed/26986203
[1.7] https://www.ncbi.nlm.nih.gov/pubmed/8637139/
[1.8] https://www.has-sante.fr/portail/upload/docs/application/pdf/2018-06/reco266_rbp_borreliose_de_lyme_cd_2018_06_13__recommandations.pdf

2. Too narrow an evidence base

The guidelines were developed with too narrow an evidence base. Only “full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost–utility, cost-effectiveness, cost–benefit and cost–consequences analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially includable as health economic evidence”. No use was made of in-vitro or animal studies. Studies published in languages other than English were not reviewed. Studies published before 2001 or after 3 July 2017 and studies from non-OECD countries or the US were also excluded. The limitations in what was considered includable means that much good science has been missed and the recommendations have been made without sufficient evidence. When a significant portion of the scientific literature originates from the USA, excluding that has resulted in very little evidence and much of what has included has been deemed low quality.

In the absence of good quality human studies, in vitro evidence and evidence from animal studies could be used to inform decisions. There are plenty of studies showing persistence with recommended drugs [e.g., 2.1, 2.2], including a very convincing human autopsy study [2.3].

[2.1] https://www.ilads.org/wp-content/uploads/2018/07/CLDList-ILADS.pdf
[2.2] https://www.ncbi.nlm.nih.gov/pubmed/31739409
[2.3] https://www.ncbi.nlm.nih.gov/pubmed/31614557

3. Failure to indicate prevalence

The European Commission acknowledges that “Lyme borreliosis is a prevalent tick-borne disease in Europe” [3.1]. A recent study estimated that the Scottish incidence is 37.3 per 100,000 per annum (approx. 2028 cases per annum).

However, the NICE Guidelines fail to give any idea of prevalence of Lyme stating “this information is currently not available” … but then goes on to say “The available data suggests there are areas of higher and lower prevalence”.

Lyme disease is described as an uncommon cause of certain symptoms. No emphasis is placed on the fact that when this constellation of symptoms occur simultaneously, Lyme disease may be a common cause.

[3.1] https://ecdc.europa.eu/en/news-events/european-commission-updates-communicable-disease-surveillance-list-lyme

4. Failure to acknowledge alternative transmission methods

NICE do not acknowledge alternative transmission methods.

As far back as 1986, a study concluded that "B. burgdorferi can be transmitted by direct contact without an arthropod vector" [4.1]. It has been found in breast milk and found to survive in urine of mice [4.2]. It has been suggested it could contaminate the food chain via cow’s milk [4.3]. It has been found that borrelia can survive blood bank conditions [4.4]. A number of studies have found that transmission can take place from insects other than ticks, including mosquitos and fleas [4.5].

Congenital Lyme disease has been acknowledged by the US CDC [4.6]. However, the NICE Guidelines give false reassurance about the risk of congenital Lyme disease being ‘very low’ when more research is needed in this area. Unlike the NICE guidelines, the French Protocol for Diagnosis and Care of tick-borne diseases (TBDs) recognizes the reality of congenital Lyme and the need for preventing the devastation it causes [4.7]. The French Protocol recommends treatment for pregnant woman who show symptoms, even when seronegative.

By not considering a wider scope, NICE also failed to recommend screening of blood products for babesia. The CDC in America are actively looking at preventing transmission of babesia through the blood supply and developing a screening test [4.8].

[4.1] https://www.ncbi.nlm.nih.gov/pubmed/3513648
[4.2] https://www.ncbi.nlm.nih.gov/pubmed/7648832
[4.3] http://jfoodprotection.org/doi/pdf/10.4315/0362-028X-54.7.532?code=FOPR-site
[4.4] https://www.ncbi.nlm.nih.gov/pubmed/2349627
[4.5] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC266646/
[4.6] https://www.cdc.gov/lyme/transmission/index.html

[4.7] https://www.has-sante.fr/portail/upload/docs/application/pdf/2018-06/reco266_rbp_borreliose_de_lyme_cd_2018_06_13__recommandations.pdf
[4.8] https://www.cdc.gov/parasites/babesiosis/resources/babesiosis_policy_brief.pdf

5. Lack of acknowledgement of full spectrum of symptoms

The NICE guidelines do not acknowledge the full spectrum of symptoms.

On June 18, 2018 the World Health Organization (WHO) issued the 11th revision of the International Classification of Diseases or ICD11. Although WHO has recognized Lyme borreliosis to be a 'disease of consequence' since the 1990s, new codes have been established for life-threatening complications from Lyme borreliosis, allowing serious complications to be officially recognized by the WHO.

The new ICD11 codes now include dementia and central nervous system demyelination due to Lyme borreliosis. They also recognize: Disseminated Lyme borreliosis, Lyme Neuroborreliosis, Lyme Carditis, Ophthalmic Lyme borreliosis, Lyme arthritis, Late cutaneous Lyme borreliosis, Other specified disseminated Lyme borreliosis, Disseminated Lyme borreliosis, unspecified, Infectious panuveitis in Lyme disease and Infectious intermediate uveitis in Lyme disease [5.1]
[5.1] http://www.ticscotland.org.uk/lymeinidc11

6. No differentiation between borrelia species

Research related to borrelia burgdorferi has been applied to all forms of borrelia, without taking into account the differences introduced by different species.

There are two issues: all strains may not be tested for; and treatment may be different for different strains.

A study in Scotland of local Highland isolates identified 6 strains which differed from the reference strains. There may therefore be other unidentified strains in Scotland which are not being tested for [6.1].

8% of infected ticks in Scotland are infected with Borrelia valaisiana. Borrelia valaisiana has been found to have a different mechanism of action [6.2]. In fact, it is often said that Borrelia valaisiana does not cause human illness and is not currently tested for, but there is at least one report in the literature on this [6.3]. If no testing is done, how will other examples be found?

Borrelia miyamotoi exists in Scotland [6.4]. However there are issues with testing [6.5] and there is currently no accredited test in Scotland [1.5].
[6.1] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1186912/
[6.2] http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0053659
[6.3] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3320289/

[6.4] https://wwwnc.cdc.gov/eid/article/23/3/16-1397_article
[6.5] http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0191725

7. No differentiation between early and late disease

Many patients are not treated promptly and yet there is no differentiation in treatment between early and late disease. Many studies looking at early infection are being used to dictate treatment in late disease, when patient experience shows it is woefully inadequate.

In 2017, in a study in primates to comprehensively examine pathology associated with persistence of B. burgdorferi in the late stage of Lyme disease following antibiotic therapy, they found that, when treatment was delayed until 16 weeks after the bite, no monkeys were cured with antibiotic treatment which matched or exceeded the treatment recommendations made in the NICE guidelines [7.1].

A recent pilot study published after the draft NICE guidelines were issued, provides evidence for persistence in humans after treatment [7.2], corroborating patient experience. A recent autopsy study found borrelia in four different organs after a patient died after 16 years of treatment when antibiotics were withdrawn [2.3].

Given the regular lack of diagnosis in the first few weeks, patients need differentiation of treatment between early and late disease.
[7.1] http://ajp.amjpathol.org/article/S0002-9440(17)30894-5/fulltext
[7.2] http://www.mdpi.com/2227-9032/6/2/33

8. Imperfect testing

Patients want their multiple infections to be diagnosable in order to allow correct treatment. Co-infections such as multiple species of Anaplasma, Bartonella and Babesia are treatable but are not being picked up by testing and so no treatment is being provided.

NICE have acknowledged that Lyme testing needs to be researched but have provided no avenue for patients to get treatment in the meantime. Because of the narrow scope, they have not acknowledged the large number of possible infections and the lack of testing for those, or the fact that new infectious agents are being discovered all the time and so there will not be perfect testing any time soon.

NICE suggest using the IR6 ELISA test for Lyme testing. However, they do not acknowledge that multiple infections might cause immune suppression to the extent that the ones for whom tests are negative because antibodies are not produced might be the most ill patients.

It has been known since 1988 that some patients with chronic Lyme disease do not develop antibodies, when a study in the New England Journal of Medicine [8.1]

concluded that although chronically ill "patients had clinically active disease, none had diagnostic levels of antibodies to B. burgdorferi on either a standard enzyme-linked immunosorbent assay or immunofluorescence assay. On Western blot analysis, the level of immunoglobulin reactivity against B. burgdorferi in serum from these patients was no greater than that in serum from normal controls".

Patients therefore want a test which addresses this. There are multiple possibilities, including:

1. Direct detection methods such as PCR, DNA, etc., do not rely on antibodies
2. T-cell tests such as Elispot detect a different immune response and so might be useful.
3. The Te?ted TickPlex Plus test looks for antibodies to round-body forms of borrelia as well as the spirochaete form. It also looks for multiple co-infections in a single test [8.2].

We want a reliable test to tell us when the infection has been successfully eradicated and when further treatment is or is not needed.

In a very useful review of the European situation, it has been stated that "Development of new diagnostic methods is badly needed. New PCR methods and new genomic techniques, such as high throughput sequencing, could prove promising in identifying the complex mix of microbial agents that are probably involved" [8.3].

However, patients also want it recognised that research has shown that borrelia can be harboured in the body in localised areas and resurge after many months, thus meaning that even direct detection methods will not be fully accurate if the wrong sample is taken.

In the French National Plan [8.4], they state they have a single tick-borne infection test covering 59 different tick-borne infections. Scotland has nothing remotely like this.

[8.1] https://www.nejm.org/doi/full/10.1056/NEJM198812013192203
[8.2] https://tezted.com/products/#plus-plan
[8.3] https://www.frontiersin.org/articles/10.3389/fcimb.2014.00074/full
[8.4] http://solidarites-sante.gouv.fr/IMG/pdf/plan_lyme_281216_aes_-_2.pdf

9. No acknowledgement of morphological and persistent forms

The guidelines recommend use of single antibiotics. There is no acknowledgement of the different morphological forms of Lyme and their different responses to antibiotics [9.1]. As far back as 1995, it was known that some drugs induce borrelia to transform into the different morphological forms [9.2]. This research was built on in 2011 in a paper [9.3] which concludes that “Antibiotics have varying effects on the different morphological forms of B. burgdorferi. Persistence of viable organisms in round body forms and biofilm-like colonies may explain treatment failure and persistent symptoms following antibiotic therapy of Lyme disease.”

There is also no acknowledgement of the build-up of biofilm in chronic illness [9.4]
[9.1] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4505243/
[9.2] https://www.ncbi.nlm.nih.gov/pubmed/7698837/
[9.3] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3132871/
[9.4] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3480481/

10. No guidance on immune support

There are no recommendations for immune support, control of inflammation, or nutritional support required to allow the body to cope. There is no recognition that genetics play a part in the disruption of the body's biochemical pathways. There is no recognition that alternative therapies might play a part in healing.

Lyme Disease can suppress the immune system and allow latent infections to come to the fore. Examples include mycoplasma pneumoniae, chlamydia pneumoniae, Epstein Barr and Herpes viruses. Some co-infections are developing antibiotic resistance and "reducing the level of immunosuppression when possible would appear to be a desirable strategy" [10.1].
[10.1] https://www.ncbi.nlm.nih.gov/m/pubmed/20047477/

11. No recommendations for chronic illness

Many are never treated promptly following a tick bite or an EM rash and chronic illness sets in which appears to be much more complex to treat.

The guideline states that ‘most people recover completely’. Patients argue that this is highly misleading and simply not the case. This statement affects the way both doctor and patient see the severity of Lyme disease and fails to acknowledge that some people never recover and are severely disabled.

The guideline highlights the weak evidence base for current treatment protocols: “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.”

There is an acknowledgment that treatment for Lyme disease may fail and that the infection can persist between a first and second course of antibiotics but then there is a lack of clarity on persistence beyond two courses of treatment. The guideline states that it may take “months or years” for symptoms to resolve after treatment and that symptoms may be a result of “permanent damage” from Lyme disease, but provides no method of distinguishing that from chronic infection.

It suggests that only a small number of people experience “treatment failure”. However, there is a large and growing population of patients suffering from progressively worsening and debilitating symptoms who are not acknowledged in the guideline. Thousands of patients in the UK are still desperately unwell following short

courses of antibiotics. The Lyme Disease UK patient support forum now has over 11,000 members.

The guideline provides no recommendations for those with chronic illness other than to refer to a specialist. However, there is no access to specialists in the UK.

In a recent UK paper, it was suggested that patients who are chronically ill but seronegative "have a different disease from Lyme disease and therefore an alternative name, chronic arthropod-borne neuropathy (CAN)" [11.1]. However, the narrow scope of the guidelines means no account is taken of those with such chronic illness.

Patients who are so chronically ill believe they may have multiple tick-borne co-infections.
[11.1] https://www.cambridge.org/core/journals/epidemiology-and-infection/article/lyme-borreliosis-in-southern-united-kingdom-and-a-case-for-a-new-syndrome-chronic-arthropodborne-neuropathy/C8F77270AB57055A09EB141228D47632

12. Lack of specialists

The guideline frequently states that patients should be referred to specialists whereas the reality is, there are no Lyme disease specialists within the NHS. Consultants have in the past used the outdated IDSA guideline or British Infection Association position paper to refuse treatment. Patients are left abandoned without help. The same is happening with the NICE guidelines.

There is no recommendation for development of specialist service provision, where long-term and late diagnosed disease can be treated and UK clinicians can gain in experience. Consultant operating in silos make the patient's experience long and wandering and make it hard for consultants to draw on the experience of others.

The French National Plan proposes establishment of multi-disciplinary specialist treatment centres. Unlike NICE and other guidelines that makes infectious diseases specialists the central decision-makers in patient care, the French National Plan sees infectious diseases specialists as part of a health care team for treating those with tick-borne diseases. They would include neurologists, rheumatologists, dermatologists, psychiatrists, psychologists, pain specialists, internists, cardiologists, ophthalmologists, otolaryngologists, and endocrinologists.

13. French guidelines are better

NICE and other guidelines focus on syndromes that have not been validated and are used to dismiss the ongoing significant to severe debilitations and disabilities experienced by patients, and particularly by those patients obstructed from antimicrobial treatment options that have met internationally accepted standards. PLS (Post Lyme Syndrome) or Post Lyme Disease Treatment Syndrome (PTLDS) are such

syndromes; they explicitly deny the need for ongoing access to antimicrobials despite the evidence of persistent infections.

Other Guidelines refer to psychosomatic conditions, e.g. MUS (Medically Unexplained Symptoms) that have been repudiated by national psychiatric associations and are also used to deny medical care for biological illness. According to the French Plan [translated from French],

> 'it is necessary to abstain from the false dichotomy of 'psychosomatic OR biological/organic pathologies. … A practitioner who does not know how to treat his [Lyme, tickborne diseases] patient cannot use therapies for psychosomatic illness instead of treatment for biological/organic illness and infection. However, treatment for the psychological distress caused by such infections, as well as psychiatric conditions arising from neurological damage from the infections, may be used in addition to antimicrobial treatments for the infections and biological illness. Such psychological or psychiatric therapies may only take place if there is a finding they would be useful and after the patient undergoes a thorough assessment by specialists [psychiatrists and neurologists].'

The French Plan has introduced the Syndrome of Persistent Polymorphic symptoms after a Tick bite (SPPT). Unlike MUS and PTLDS that deny medical treatment options for infection, SPPT explicitly provides the opportunity for access to ongoing antimicrobial treatment without positive tests results and recognizes the symptoms as most certainly not medically unexplained.

The proposed French specialist centres make no emphasis on validation of Lyme or other tick-borne diseases by infectious diseases specialists. Furthermore, the French Protocol has no stated restriction, that, until these specialized centres are established, no one can be treated beyond an arbitrary short period.
[13.1] https://www.has-sante.fr/portail/upload/docs/application/pdf/2018-06/reco266_rbp_borreliose_de_lyme_cd_2018_06_13__recommandations.pdf

14. Maintaining the status quo

The French National Plan and the associated Protocol for Diagnosis and Care have been prepared with the understanding that there is no research to allow definite decisions to be made and so open-ended treatment based on treatment response is recommended. They have plans to record treatment response to different treatments so that data can be built up. Their approach allows for 2-yearly review of the recommendations so that they can be gradually refined as evidence is built up.
As an example of the result of French policy, a letter has been published recently stating "A controversy continues regarding the reality of a chronic form of Lyme disease. Chronic Lyme disease can present as a 'post-Lyme syndrome' explained by inflammatory and immunological phenomena, or as a genuine 'chronic form' attributable to the persistence of the bacteria despite proper antibiotic therapy as per

the current guidelines. The current guidelines however may not be so appropriate in the latter case." [14.1]

By contrast, the NICE guidelines allow only 2 courses of a few weeks of specifically-defined treatment. This gives no opportunity to build up a database of outcomes of alternative treatment for those with chronic illness and so does not provide a constructive way forward. This is despite their scoping document stating "There is still limited understanding of the epidemiology, diagnostic tests and treatment options" and "the best treatment in late-diagnosed cases is unknown".

Patients want the French approach to be followed, developing a national plan for dealing with all co-infections, developing testing for all species, and providing treatment based on treatment response and not some arbitrary limited based on limited evidence. Patient priorities and realities will be better served by the French National Plan for Tick-Borne Diseases and associated Protocol for Diagnosis and Care than the NICE guidelines on Lyme Disease.
[14.1] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6100330/