Information Quality Request for Correction

Disclaimers Needed for Lyme Disease Case Definition

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Patients and doctors look to the Centers for Disease Control and Prevention (CDC) for information on and guidance about Lyme disease, including diagnostic criteria. Unfortunately, there is confusion among healthcare providers and health insurers regarding use of the Lyme disease surveillance case definition for diagnosis. Therefore, pursuant to the *HHS Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated to the Public*[1] the undersigned individuals and organizations request that CDC:

1. Include a disclaimer that the case definition for Lyme disease is intended *for surveillance purposes only* everywhere the case definition is published.
2. Include a disclaimer that the case definition for Lyme disease is intended *for surveillance purposes only* in any publications or presentations that discuss the case definition criteria for interpretation of the two-tier test for Lyme disease.

Introduction

Lyme disease is the most common vector-borne disease in the United States, with more than 427,000 estimated new cases in 2017. According to the December 2018 report from the HHS Tick-Borne Disease Working Group, the epidemic of Lyme and related tick-borne diseases potentially costs the U.S. economy $50-$100 billion annually.

Lyme disease is a clinical diagnosis, based on a patient's medical history, symptoms, and exposure to ticks. Since Lyme disease diagnostic tests are relatively insensitive, a negative test result does not necessarily mean a patient does not have Lyme. Reasons for a negative test include lack of time for antibodies to develop, a suppressed immune system, or infection with a strain of Lyme the test doesn't recognize.

A surveillance case definition is a set of uniform criteria used to define a disease for public health surveillance purposes. According to CDC, "Surveillance case definitions are NOT intended to be used by healthcare providers for making a clinical diagnosis or determining how to meet an individual patient's health needs."

According to the case definition for Lyme disease, most patients must either present with an erythema migrans (EM, also known as a bull's-eye rash) or have a positive result on the two-tier serology test for a case to be counted for surveillance purposes. The two-tier serology test comprises the Enzyme Linked Immuno-Sorbent Assay (ELISA) and Western Blot tests.

In high-incidence states, an EM rash alone is sufficient to count as a confirmed case of Lyme. In low-incidence states, patients without an EM rash must test positive either by culture or by the two-tier test. Patients who have at least one late manifestation of Lyme disease, such as Bell's Palsy or central nervous system involvement, and test positive are counted as confirmed cases in both low and high incidence states.

Because many patients do not experience a rash[2] and do not have other objective manifestations, and because culture tests are expensive and insensitive, the case definition relies more heavily on the two-tier test than on other diagnostic methods.

Background

The two-tier testing algorithm was adopted at the Second National Conference on Lyme disease testing in Dearborn, Michigan in 1994. This test is an indirect assay that measures the immune response but *does not confirm* the presence of an infection.

The first step in the two-tier test is an ELISA screening test. If the ELISA is negative, no further testing is recommended. If the ELISA is positive or equivocal, a Western Blot is performed for confirmation. The Western Blot detects antibodies against a set of preselected protein antigens. Antibody reactivity to these antigens is indicated by "bands" An antigen is considered present if a band has intensity equal to or greater than a control band. IgM antibodies develop early in the infection during the acute phase, and IgG antibodies develop later in the disease. Currently, the surveillance criteria for Lyme disease requires at least 2 out of 3 IgM bands or 5 out of 10 IgG bands.

The poor accuracy of the two-tier test for Lyme disease has been a point of contention for years. According to CDC, the two-tier test is inaccurate in the early stages of the disease and should not be relied upon for at least 6 weeks after a tick bite. CDC asserts that the two-tier test is highly accurate later in the disease, but a systematic meta-analysis of 20 years of published data showed a mean sensitivity of only 35.4% in the acute stage and 64.5% in the convalescent stage, with an overall sensitivity of only 59.5%.[3] By comparison, the sensitivity for the HIV/AIDS antibody test is greater than 99%.

The case definition criteria for the two-tier test is narrow by design so there will be few false positives. This way, CDC can be sure that positive results are true cases of Lyme disease. However, CDC acknowledges that the true number of Lyme cases is at least 10 times greater than the number of cases reported according to the surveillance criteria.

Since CDC requires a set threshold number of bands for surveillance purposes, many patients will get false negative results even if they test positive for one or more Lyme-specific bands. The unreliability of the two-tier test is compounded by widespread misconception by healthcare providers and insurers that patients must test positive according to the surveillance criteria to confirm they have a true case of Lyme disease.

Current Situation

Despite CDC guidance, many physicians continue to rely on the case definition for Lyme disease to interpret results of the two-tier test so many cases of Lyme go undiagnosed. Many health insurers also rely on the case definition for Lyme disease to determine coverage. The result is that large numbers of patients who have Lyme disease are misdiagnosed and denied medically necessary treatment and insurance coverage. This situation worsens the Lyme epidemic and increases the financial impact on our country in terms of lost productivity, disability, and increased medical expenses.

In report 107-84 for CDC's FY 2002 appropriations bill[4], the Senate Appropriations Committee addressed misuse of the Lyme disease case definition with the following directive:

> "The Committee is distressed in hearing of the widespread misuse of the current Lyme disease surveillance case definition. While the CDC does state that "this surveillance case definition was developed for national reporting of Lyme disease: it is NOT appropriate for clinical diagnosis," the definition is reportedly misused as a standard of care for healthcare reimbursement, product (test) development, medical licensing hearings, and other legal cases. The CDC is encouraged to aggressively pursue and correct the misuse of this definition. This

includes issuing an alert to the public and physicians, as well as actively issuing letters to places misusing this definition."

Unfortunately, years after this directive was issued, widespread misuse of the case definition for Lyme disease continues to be a serious problem and CDC continues to disseminate information that encourages use of the surveillance criteria to interpret results of the two-tier test for clinical diagnosis. Therefore, in 2018, the Senate issued a follow-up directive for CDC to issue a report on how it has been addressing the misuse of the Lyme disease case definition:

Senate Report 115-150 for CDC's FY 2018 appropriations bill[5] states:

> "Further, the Committee is concerned by reports that cases of Lyme disease are under-reported and encourages CDC to re-evaluate surveillance criteria used to track cases of the disease while assisting States to more accurately evaluate prevalence. The Committee requests a report within 180 days of enactment of this act on how CDC is examining the potential misuse of the Lyme disease case definition."

More than a year after this bill was enacted, however, CDC has not produced the report requested by the Appropriations Committee. In fact, CDC continues to disseminate misleading information that encourages healthcare providers to rely on the Lyme disease case definition for interpreting the results of the two-tier test.

In a December 2018 report to Congress[6], the HHS Tick-Borne Disease Working Group made the following recommendation to address the situation:

> "The Lyme disease surveillance criteria are not to be used alone for diagnostic purposes; public health authorities shall annually and when opportune (such as during Tick-Borne Disease Awareness Month) communicate this and inform doctors, insurers, state and local health departments, the press, and the public through official communication channels, including the CDC's Morbidity and Mortality Weekly Report (MMWR)."

To date, no such notices have been issued by CDC or other HHS agencies.

Information to be Corrected

The CDC web pages for the 2008 and 2011 Lyme disease case definition include the following disclaimer:

> "This surveillance case definition was developed for national reporting of Lyme disease; it is not intended to be used in clinical diagnosis."

However, the CDC web page for the Lyme Disease 2017 Case Definition[7] lacks this disclaimer. It is unclear why this disclaimer was dropped for 2017.

While there is the following disclaimer on the web page for the National Notifiable Diseases Surveillance System (NNDSS), it is not specific to Lyme disease.[8]

> "Surveillance case definitions are not intended to be used by healthcare providers for making a clinical diagnosis or determining how to meet an individual patient's health needs."

Even though this disclaimer applies to the Lyme disease case definition, many visitors to the web page for the case definition may miss it because they may navigate to the page directly rather than through the main NNDSS web page.

Impact

CDC's omission of a disclaimer that the surveillance case definition for Lyme disease is not appropriate for clinical diagnosis increases the chance that physicians who have been relying on the case definition for diagnosing patients will not receive the correct information, and patients with Lyme disease will continue to be misdiagnosed.

In addition, the online CME (continuing medical education) credit offered by Medscape, LLC, in providership with Emerging Infectious Diseases, encourages physicians to rely on the surveillance case definition for interpretation of the two-tier test for diagnosis of Lyme disease. This situation exacerbates the problem of Lyme disease sufferers not receiving a proper diagnosis and treatment, potentially leading to chronic Lyme disease and serious health effects with far greater treatment costs.

Recommended Actions

Given the potential for harm to patients who are misdiagnosed and denied treatment due to misuse of the surveillance case definition, and in light of the directives from Congress for CDC to aggressively correct misuse of the case definition for Lyme disease, we request that CDC immediately take the following actions:

1. Include the following disclaimer wherever the case definition for Lyme disease is published:

   "This surveillance case definition was developed for national reporting of Lyme disease; it is NOT intended to be used in clinical diagnosis."

   A web page that needs this disclaimer is:
   https://wwwn.cdc.gov/nndss/conditions/lyme-disease/case-definition/2017/

2. Include the following disclaimer on any web pages and in any publications that describe the case definition's interpretation criteria for the two-tier test:

   "The surveillance case definition for Lyme disease was developed for national reporting; it is NOT intended to be used in clinical diagnosis. In addition, interpretation of the two-tier test for clinical diagnosis does not require a specific number of positive IgM or IgG bands on the Western Blot test."

   Web pages that need this disclaimer include the following:
   www.cdc.gov/lyme/diagnosistesting/labtest/twostep/index.html

   www.cdc.gov/lyme/diagnosistesting/labtest/twostep/westernblot/index.html

3. Publish an alert in the CDC Morbidity and Mortality Weekly Report (MMWR) that the surveillance case definition for Lyme disease is for national reporting only and is NOT intended to be used in clinical diagnosis.

4. Include the following disclaimer with any CME courses for Lyme disease offered by Medscape, LLC, in providership with Emerging Infectious Diseases:

   "The surveillance case definition for Lyme disease is intended for national reporting and is NOT to be relied on for clinical diagnosis. Interpretation of the two-tier test for clinical diagnosis of Lyme disease does not require a specific number of positive IgM or IgG bands on the Western Blot."

5. Send letters to health insurance companies, informing them of the disclaimers listed above.

Conclusion

Lyme disease is at epidemic proportions, yet cases remain underreported. Confusion exists among healthcare providers concerning guidance from CDC on interpretation of the two-tier test for clinical diagnosis.

While the case definition for Lyme disease is narrow by design and intended for surveillance purposes, it was not intended to be used by healthcare providers for clinical diagnosis. In addition, the case definition relies heavily on the two-tier serology test, which can give varying and unreliable results, partly due to interpretation criteria. As a result, the number of Lyme cases in this country is far greater than what the case definition for surveillance reflects.

It is imperative, therefore, that CDC immediately issue the disclaimers described in this paper regarding the case definition for Lyme disease and the case definition interpretation criteria for the two-tier test. These disclaimers should appear everywhere the case definition is published, including in any publications or presentations that describe the case definition interpretation criteria for the two-tier test.

CDC should also notify health insurance companies of the aforementioned CDC disclaimers so Lyme disease patients will be able to submit medical claims with potentially fairer consideration.

Thank you for your prompt attention to this matter. We look forward to your response and action.

Complainant

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References

[1] HHS Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated to the Public. https://aspe.hhs.gov/report/hhs-guidelines-ensuring-and-maximizing-quality-objectivity-utility-and-integrity-information-disseminated-public

[2] An Update on the Diagnosis and Treatment of Early Lyme Disease: "Focusing on the bull's eye, you may miss the mark". www.ncbi.nlm.nih.gov/pubmed/17945460

[3] Commercial Test Kits for Detection of Lyme Borreliosis: A Meta-Analysis of Test Accuracy. www.ncbi.nlm.nih.gov/pubmed/27920571

[4] Senate Report 107-84 to Accompany S. 1536 for FY 2002. www.congress.gov/congressional-report/107th-congress/senate-report/84

[5] Senate Report 115-150 to Accompany S. 1771 for FY 2018 www.congress.gov/congressional-report/115th-congress/senate-report/150/1

[6] HHS Tick-Borne Disease Working Group Report to Congress https://www.hhs.gov/sites/default/files/tbdwg-report-to-congress-2018.pdf

[7] Lyme Disease 2017 Surveillance Case Definition https://wwwn.cdc.gov/nndss/conditions/lyme-disease/case-definition/2017/

[8] National Notifiable Diseases Surveillance System, case definitions https://wwwn.cdc.gov/nndss/case-definitions.html