Nebraska Department of Health and Human Services

HEALTH ALERT NETWORK Advisory

NEBRASKA
Good Life. Great Mission.
DEPT. OF HEALTH AND HUMAN SERVICES

TO: Primary care providers, infectious disease, laboratories, infection control, and public health

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RE: LYME DISEASE IN NEBRASKA

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The arrival of spring marks the beginning of another tick season. In the interest of public health and prevention, our office seeks to inform Nebraska health care providers about Lyme disease, including proper testing of suspect cases and treatment.

Key messages for Nebraska clinicians:

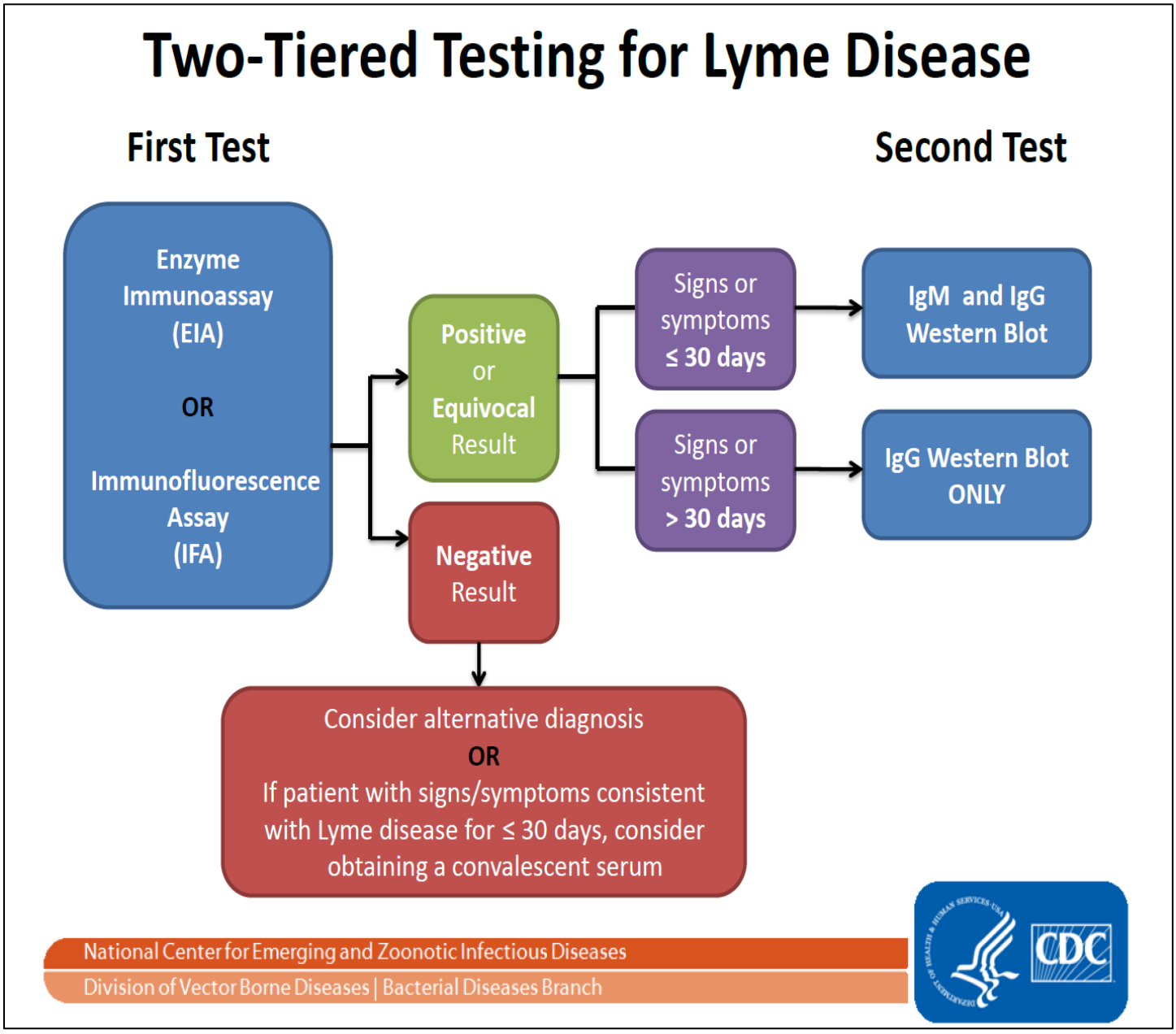
Lyme Disease

Lyme disease is transmitted by the tick *Ixodes scapularis* (black-legged tick or deer tick). For the first time in Nebraska, established populations (meeting CDC criteria) of this tick were identified during 2019 in Douglas, Sarpy, and Saunders counties. **This fact makes it possible for Lyme disease, caused by *Borrelia burgdorferi*, to be acquired in eastern Nebraska. However, even with these established populations, Nebraska is presently considered a low prevalence state for Lyme disease. At this time, local human health risk is unknown, but clearly of increased concern.** While state and Federal support for tick surveillance field work is limited, broadened tick surveillance efforts through a partnership with entomologists at Nebraska Department of Agriculture and the University of Nebraska-Lincoln is being implemented.

Lyme disease is highly regional in the United States with most cases reported from the Northeast and upper Midwest. In 2019, Nebraska reported 9 (3 confirmed, 6 probable) cases to the national reportable disease system at the CDC. Most cases where exposure could be determined had exposure/acquisition in regions of the country where this tick is highly endemic. However, two of the reported probable cases, after epidemiological investigations, revealed that the infections were most likely acquired in eastern Nebraska. Due to these two identified probable cases and because Nebraska is in a zone where the tick vector appears to be continuing to expand further**, providers suspecting Lyme disease must be vigilant and get good patient histories including: any prior travel 30 days before symptom onset, reported tick attachments/bites, reported exposure to tick habitat (e.g. tall grass or wooded areas), etc. Additionally, providers should take great care to order the correct serologic tests in the proper order**.

Serologic testing for Lyme disease is currently the best method for lab diagnosis. The standard method **requires a strict two-step process.** The first required test is either an enzyme immunoassay (EIA) or immunofluorescence assay (IFA). If this test yields negative results, the provider should consider an alternative diagnosis. Or in cases where the patient has had symptoms for less than or equal to 30 days, the provider may treat the patient and follow up with a convalescent serum. If the first test yields positive or equivocal results, two options are available: 1) if the patient has had symptoms for less than or equal to 30 days, an IgM and IgG Western blot is performed; 2) if the patient has had symptoms for more than 30 days, the IgG Western blot is

performed. **The IgM should not be used if the patient has been ill for more than 30 days**. Positive serologic evidence **requires both the EIA (or IFA) and Western blot to be positive**. This testing algorithm optimizes sensitivity and specificity in untreated patients (https://www.cdc.gov/lyme/healthcare/index.html).



Understanding the EIA Test

Several types of EIA tests exist. Validated and FDA-approved EIAs include "ELISA" (enzyme-linked immunosorbent assay) and "ELFA" (enzyme-linked fluorescent immunoassay). Lyme disease testing measures a person's antibody to the bacteria that cause Lyme disease. EIA tests are designed to be ultra "sensitive", meaning that when they are used properly, almost everyone with Lyme disease will test positive. It is also possible, however, to test positive with an EIA test even when you do not have Lyme disease. This can occur because of other medical conditions, including but not limited to:

- Tick-borne relapsing fever
- Syphilis
- Anaplasmosis (formerly known as granulocytic ehrlichiosis)
- Leptospirosis
- Some autoimmune disorders (e.g., lupus)

- Bacterial endocarditis
- Infection with *Helicobacter pylori*, Epstein Barr virus, or *Treponema denticola* (bacteria found in the mouth that can cause gum disease and/or infection after dental procedures)

For this reason, providers should verify any "positive" or "equivocal" (indeterminate) EIA results by performing an immunoblot test such as a Western blot. The Western blot or other FDA-approved type of immunoblot can help distinguish patients who have Lyme disease from those with other conditions.

Understanding the Immunoblot Test

The immunoblot is a laboratory test that looks for antibodies the body makes against different molecules, or "antigens," that are part of the *Borrelia burgdorferi* bacteria. Western blots were the first type of immunoblot developed for Lyme disease testing. Later, a striped type of immunoblot was approved by the FDA that does not require human interpretation of bands.

Practically speaking, the test produces something that looks like a bar code used on grocery items, with several lines or "bands". Each line represents antibodies to a different component of the bacteria. As with bar codes, the presence of any one or two lines is not particularly meaningful. Instead, it is the combination of multiple, specific lines that identifies the infection as being due to *Borrelia burgdorferi*.

Immunoblot tests for Lyme disease testing can detect two different classes of antibodies: IgM and IgG. IgM antibodies are made sooner, so testing for them can be helpful for identifying patients during the first few weeks of infection. The downside of testing for IgM antibodies is that they are **more likely to give false positive results**. Tests for IgG antibodies are more reliable, but can take 4-6 weeks for the body to produce in large enough quantities for the test to detect them. This process is complicated and often difficult to understand. Just remember the following:

- The immunoblot **should not** be run without first performing an EIA or IFA.
- The immunoblot **should not** be run if the EIA or IFA tests are negative.
- A positive IgM immunoblot is only meaningful during the first 4 weeks of illness
- If a patient has been ill for longer than 4-6 weeks and the IgG immunoblot test is negative, it is unlikely that he or she has Lyme disease, even if the IgM immunoblot is positive.

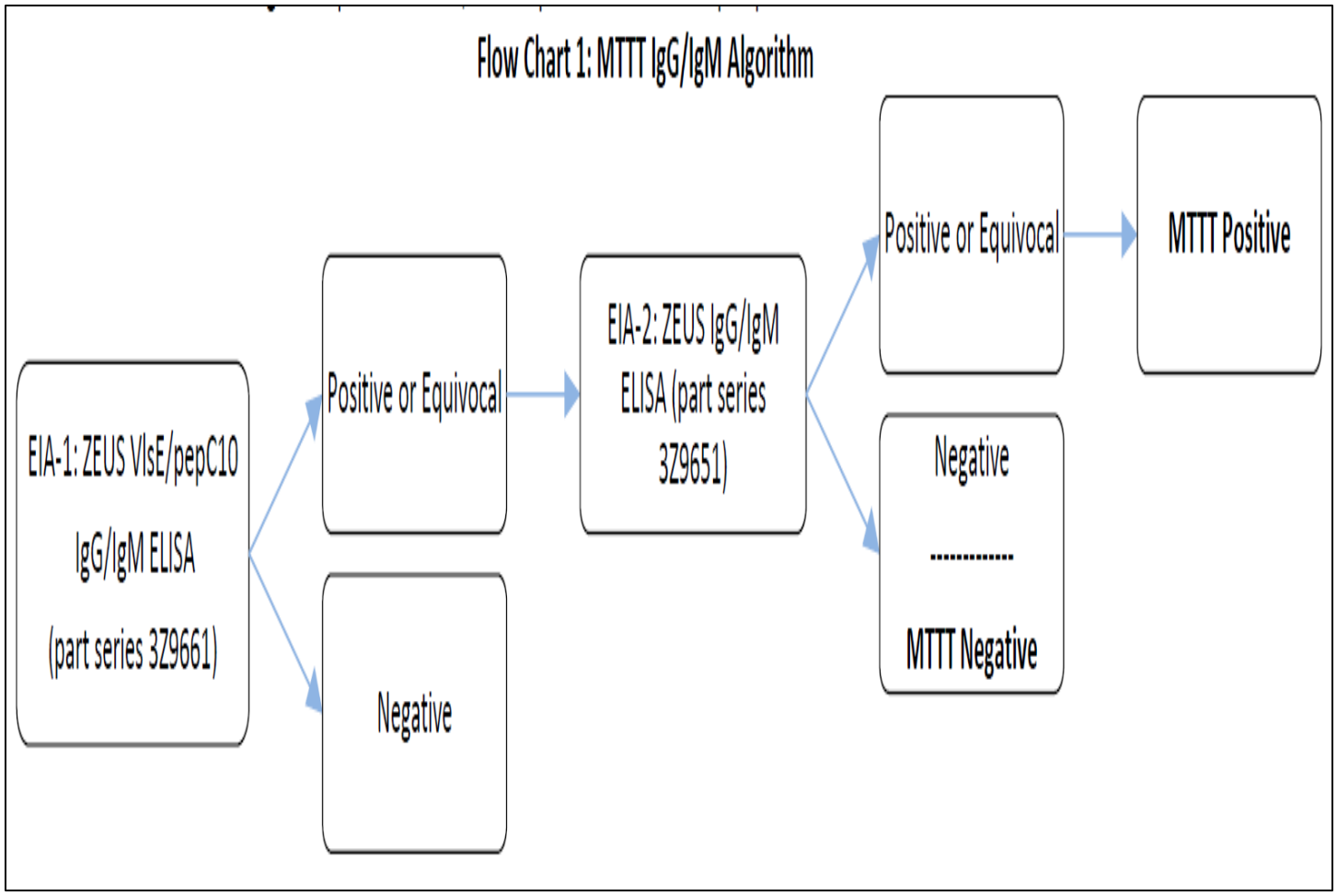
Note on test result interpretation: It is not correct to interpret a test result that has only some bands that are positive as being "mildly" or "somewhat" positive for Lyme disease. The criterion that requires at least 5 IgG bands reflects the fact that people with Lyme disease have at least 5 antigens (specific molecules) detectable.

Updated CDC Recommendation for Serologic Diagnosis of Lyme Disease

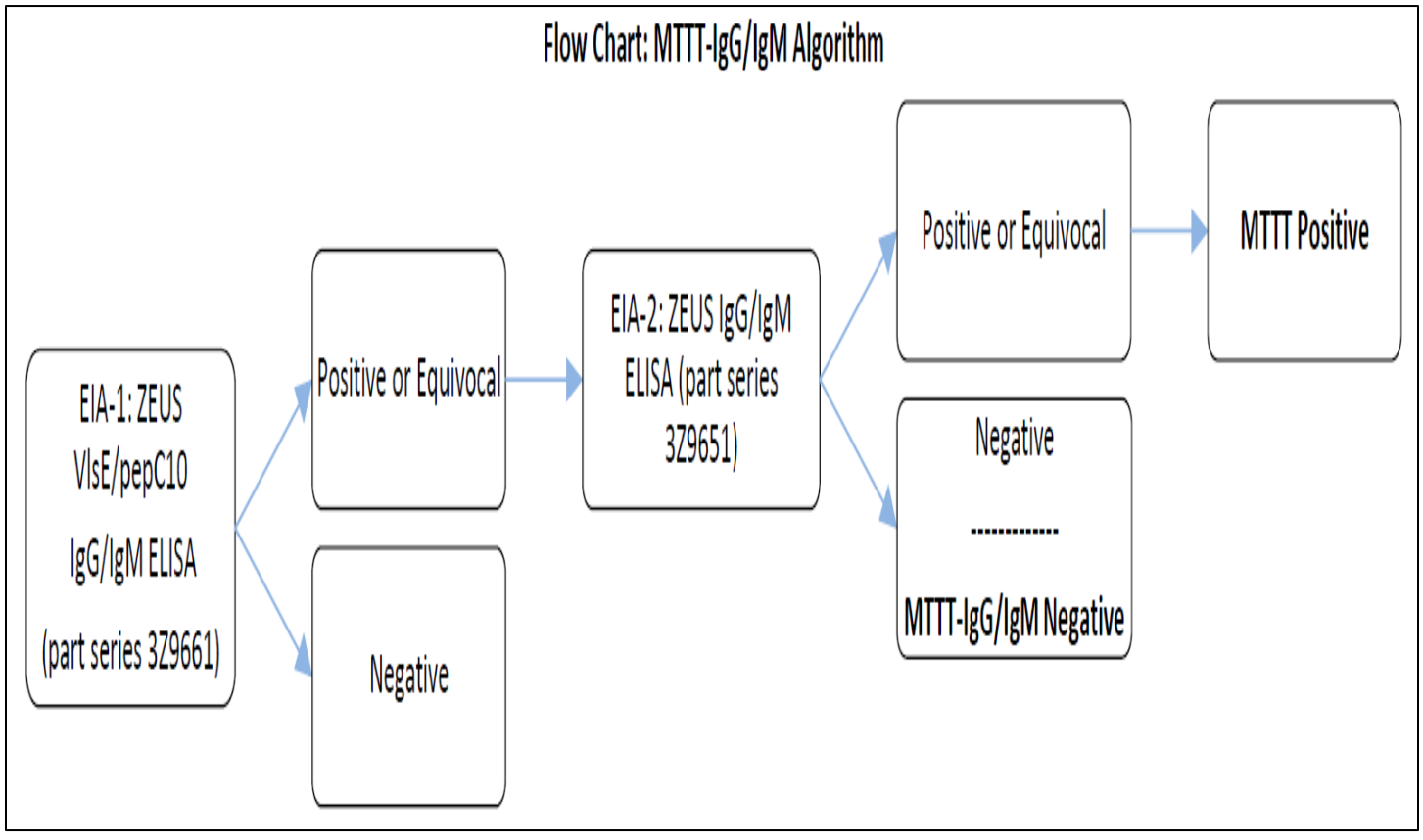
In 2019 CDC updated their recommendations regarding serologic diagnosis of Lyme disease to include a **modified standard method** in addition to the standard two-tier system. This method still requires a strict two-step process. It is similar to the standard methods but uses a second EIA in place of a Western blot (https://www.cdc.gov/mmwr/volumes/68/wr/mm6832a4.htm).

This is presently only FDA approved for use on:

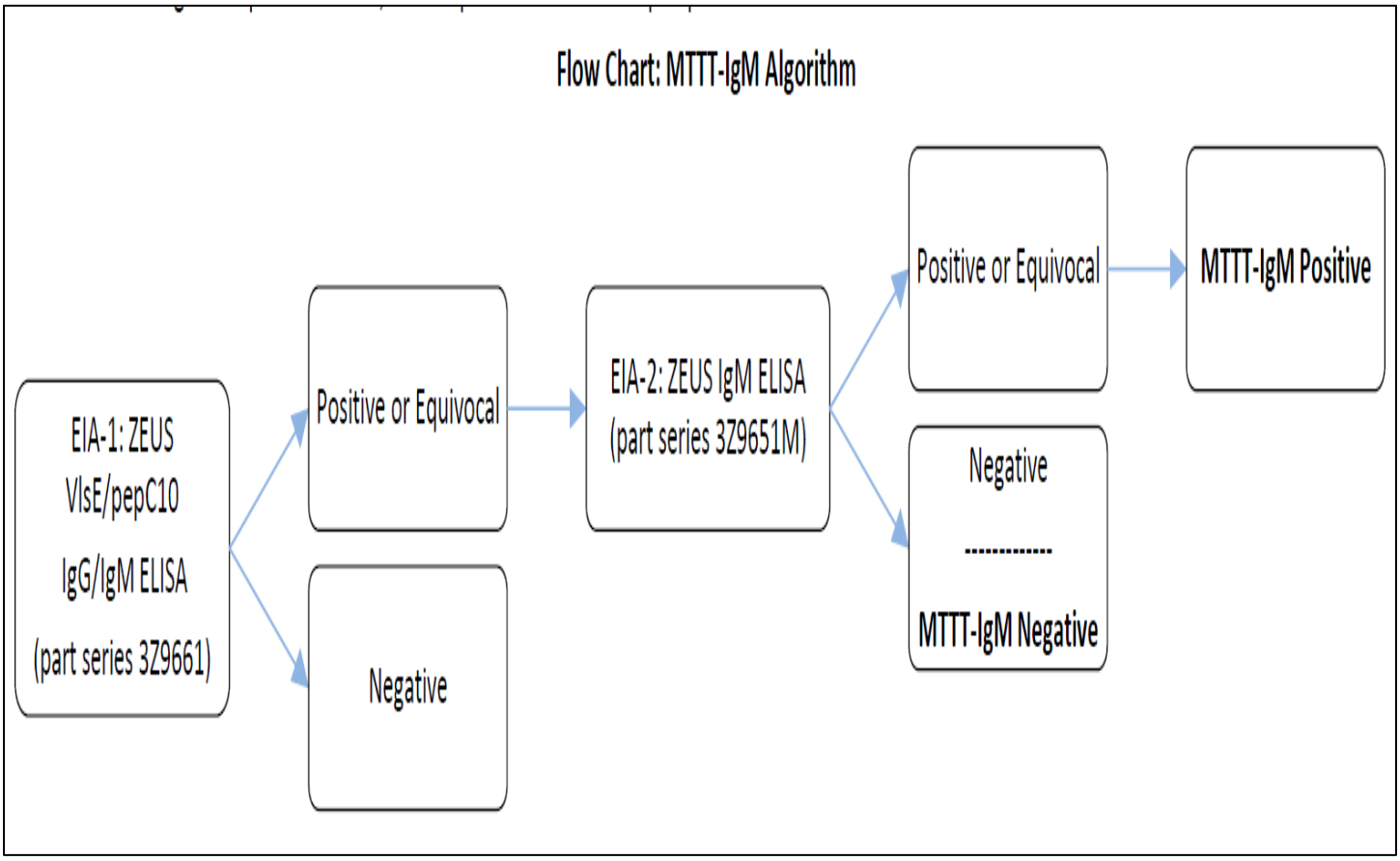
- ZEUS ELISA Borrelia VlsE1/pepC10 IgG/IgM Test System



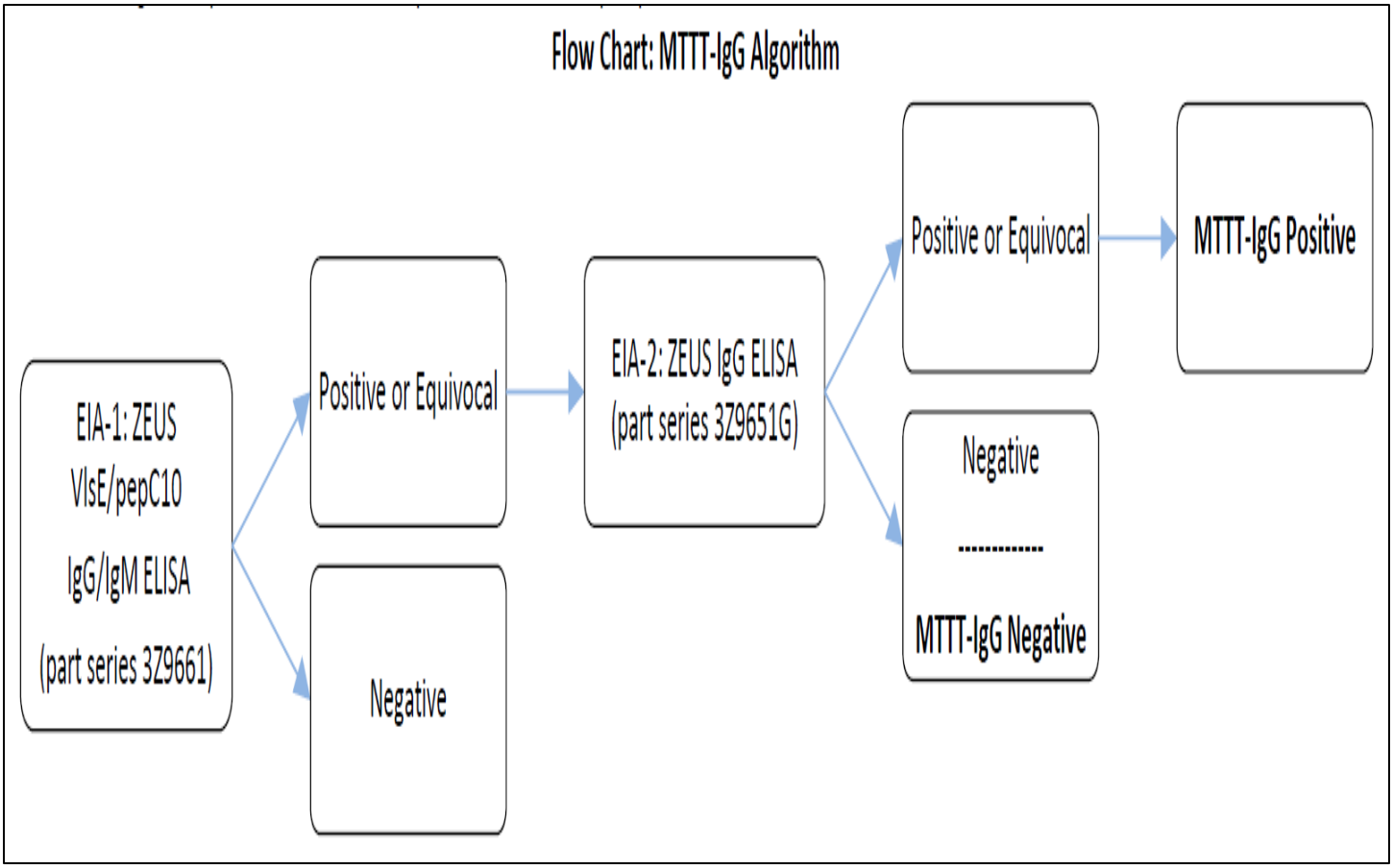
- ZEUS ELISA Borrelia burgdorferi IgG/IgM Test System



- ZEUS ELISA Borrelia burgdorferi IgM Test System



- ZEUS ELISA Borrelia burgdorferi IgG Test System



Laboratory Tests that are Not Recommended

Some laboratories offer Lyme disease testing using assays whose accuracy and clinical usefulness have not been adequately established. Examples of unvalidated tests include:

- Capture assays for antigens in urine
- Culture, immunofluorescence staining, or cell sorting of cell wall-deficient or cystic forms of *B. burgdorferi*
- Lymphocyte transformation tests
- Quantitative CD57 lymphocyte assays
- "Reverse Western Blots"
- In-house criteria for interpretation of immunoblots
- Measurements of antibodies in joint fluid (synovial fluid)
- IgM or IgG Western Blot tests without a previous ELISA/EIA/IFA

Treatment

Due to Lyme serologic tests being insensitive during the first few weeks of infection, if there is a high index of suspicion of Lyme disease, providers should not wait for lab results and delay treatment.

Per CDC guidance:

- People treated with appropriate antibiotics in the early stages of Lyme disease usually recover rapidly and completely. Antibiotics commonly used for oral treatment include doxycycline, amoxicillin, or cefuroxime axetil. People with certain neurological or cardiac forms of illness may require intravenous treatment with antibiotics such as ceftriaxone or penicillin.
- Treatment regimens listed in Table 1 are for localized (early) Lyme disease. For treatment of patients with disseminated (late) Lyme disease, please see references by Hu 2016 and Sanchez 2016. These regimens are guidelines only and may need to be adjusted depending on a person's age, medical history, underlying health conditions, pregnancy status, or allergies.
- For people intolerant of amoxicillin, doxycycline, and cefuroxime axetil, the macrolides azithromycin, clarithromycin, or erythromycin may be used, although they have a lower efficacy. People treated with macrolides should be closely monitored to ensure that symptoms resolve.

Table 1.

Age Category	Drug	Dosage	Maximum	Duration, Days
Adults	Doxycycline	100 mg, twice per day orally	N/A	10-21*
	Cefuroxime axetil	500 mg, twice per day orally	N/A	14-21
	Amoxicillin	500 mg, three times per day orally	N/A	14-21
Children	Amoxicillin	50 mg/kg per day orally, divided into 3 doses	500 mg per dose	14-21
	Doxycycline	4 mg/kg per day orally, divided into 2 doses	100 mg per dose	10-21*
	Cefuroxime axetil	30 mg/kg per day orally, divided into 2 doses	500 mg per dose	14-21

*Recent publications suggest the efficacy of shorter courses of treatment for early Lyme disease.

Post-Treatment Lyme Disease Syndrome

Physicians sometimes describe patients who have non-specific symptoms (like fatigue, pain, and joint and muscle aches) after the treatment of Lyme disease as having post-treatment Lyme disease syndrome (PTLDS) or post Lyme disease syndrome (PLDS). The cause of PTLDS is not known.

The term "chronic Lyme disease" (CLD) has been used to describe people with different illnesses. While the term is sometimes used to describe illness in patients with Lyme disease, in many occasions it has been used to describe symptoms in people who have no evidence of a current or past infection with *B. burgdorferi* (Marques 2008). Because of the confusion in how the term CLD in this field is employed, experts do not support its use (Feder et al. 2007). For more information, visit the National Institutes of Health Chronic Lyme Disease site (https://www.niaid.nih.gov/diseases-conditions/chronic-lyme-disease).

Southern Tick-Associated Rash Illness (STARI)

An erythema migrans-like rash has also been described in humans following bites of the lone star tick (*Amblyomma americanum*). The condition associated with these ticks has been names Southern Tick-Associated Rash Illness (STARI). Although the rash may be accompanied by flu-like symptoms, long-term sequelae have not been reported. Because the cause of STARI is unknown, diagnostic blood tests are not available.

The lone star tick is found from Central Texas and Oklahoma eastward across southern states, along the Atlantic coast as far north as Maine. In Nebraska, this tick is found in areas of eastern and central Nebraska and typically one of the top two most collected ticks in the state. It is a very aggressive tick readily biting humans.

It is not known whether antibiotic treatment is necessary or beneficial for patients with STARI. Nevertheless, because STARI resemble early Lyme disease, physicians often treat patients with the same antibiotics recommended for Lyme disease.

For more information please visit:

CDC Lyme Disease Page: https://www.cdc.gov/lyme/

CDC Southern Tick-Associated Rash Illness (STARI) Page: https://www.cdc.gov/stari/index.html

CDC Tickborne Diseases of the US: A Reference Manual for Health Care Providers, Fourth Edition (2017): https://www.cdc.gov/lyme/resources/TickborneDiseases.pdf

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