Lyme Disease: Fact or Fiction

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Disclosures

1. Honoraria from Pfizer for participating in meetings about Lyme vaccine.
2. Expert witness in malpractice cases.
3. Royalties from UptoDate.

Learning Objectives

- Correctly identify which patients should receive chemoprophylaxis for a tick bite.
- Correctly identify for which patients tests for Lyme disease should (and should not) be ordered.
- Correctly identify which test should be ordered to diagnose Lyme disease.
- Know how to manage a patient with erythema migrans.

LYME DISEASE
Fact or Fiction

1. Caused by the spirochete *Borrelia burgdorferi*
2. Transmitted by *Ixodes scapularis* (deer tick) and other Ixodes species
3. Pathogenesis, ecology and epidemiology are well described
4. Antimicrobial treatment is very effective
5. Complications are rare

OUTLINE

Lyme disease

a. What's old

   i. Approach to diagnosis and to treatment

   ii. Approach to patients bitten by a tick

   iii. Approach to patients with only non-specific symptoms

b. What's new

   i. New Practice Guidelines

   ii. New diagnostic test

   iii. Progress with a vaccine

Know your parasites.

Dog Tick

Deer Tick

Jordan Leland

Lone Star Tick

Luna Tick

American News X

LYME DISEASE

Clinical Manifestations

1. Early Disease (67%)
   a. Single erythema migrans
2. Disseminated Disease
   a. Early (25%)
      Multiple erythema migrans, neuritis, carditis, meningitis
   b. Late (8%)
      Arthritis

LYME DISEASE

Clinical Manifestations

1. 85-95% have the characteristic rash, erythema migrans

   a. Localized disease:

      Single erythema migrans (75%)

   b. Disseminated disease:

      Multiple erythema migrans (25%)

Lyme Disease

Erythema Migrans

Lyme Disease

Erythema Migrans

Lyme Disease

Multiple Erythema Migrans

DIAGNOSTIC TESTS FOR LYME DISEASE

1. Serology (antibodies)
2. Culture
3. Direct detection (PCR)

SEROLOGIC TESTS
FOR LYME DISEASE

1. Two-tier procedure
2. First a quantitative test, usually enzyme-linked immunosorbent assay (ELISA)
3. If ELISA is positive or equivocal (only *if)*, confirm specificity with a Western immunoblot
4. Original tests use sonicated whole bacteria (laboratory strains)

<u>LYME DISEASE</u>

Positive Result of Serology (2 tier)

1. Positive (or borderline) quantitative test result

   AND

   Positive western immunoblot

   a. IgM: 2 of 3 Bands
   b. IgG: 5 of 10 Bands

2. Misinterpretation of results common

<u>LYME DISEASE</u>

Recombinant Protein ELISA and CLIA

1. Measures antibodies against highly conserved lipoproteins (C6/C10/VlsE)
2. Hope was to replace 2-tier test with single ELISA
3. Sensitivity comparable to or better than standard whole-cell ELISA, but specificity not as good as 2-tier tests

<u>LYME DISEASE</u>
Recently Approved Tests

1. New 2-tiered algorithm in which Western blots not used at all
2. First tier test an EIA or CIA (with highly conserved surface proteins), second tier test a different EIA or CIA (eg, uses different proteins)
3. Advantages are
   a. Tests easier to perform and less expensive
   b. Results available sooner
   c. Subjective element inherent in interpreting blots can be eliminated

LYME DISEASE
Recently Approved Test

4. Sensitivity and specificity of two-tier tests good, although need wider usage to determine true values
5. However, will not have much impact on main problem with serologic testing for Lyme disease:
    a. Testing people with a low probability of having Lyme disease

LYME DISEASE SEROLOGY

Myth

1. *There are many false-negative antibody test results for Lyme disease (i.e., sensitivity is poor)*
   a. True….*but*….
   b. 85-95% of patients with Lyme disease have single or multiple erythema migrans (EM)
   c. EM usually develops 1-2 weeks after infection
   d. Antibodies detectable 3-4 weeks after infection
   e. Sensitivity poor in early Lyme disease—but not needed because of rash; Do not order
   f. Sensitivity excellent in late Lyme disease

      (100% of patients with Lyme arthritis positive)

LYME DISEASE SEROLOGY

Myth

2. Early treatment with antimicrobials may lead to false-negative serology

a. True….*but….*

b. Reason is that treatment kills the bacteria (and the antigenic stimulus to produce antibodies)

c. Cannot argue that a patient has on-going symptoms from active infection but negative serology because of previous treatment

<u>LYME DISEASE</u>

Symptoms: Test for Lyme Disease?

1. NONE
2. None of the symptoms associated with Lyme disease (headache, fever, arthralgia, fatigue, etc) is sufficiently specific by itself to make it likely symptom is due to Lyme disease
3. Unless accompanied by more specific SIGNS

Rev. Thomas Bayes (1702-1761)

1702-1761

- *Probability is that degree of confidence dictated by the evidence through Bayes's theorem. -- E.T. Jaynes*

LYME DISEASE

Serologic Tests

1. Tests for antibody should not be used for screening or for proving negative result in someone with low probability of Lyme disease
2. Order only when prior probability (“pre-test” probability) of Lyme disease is reasonably high

TEST FOR ANTIBODIES AGAINST *B. BURGDORFERI*

1. Sensitivity 95%
2. Specificity 90%
3. Pre-test probability of Lyme disease 1%

Population of 10,000

TEST FOR ANTIBODIES AGAINST *B. BURGDORFERI*

Test	Lyme Disease	No Disease	Total
Positive	95	990	1,085
Negative	5	8,910	8,915
Total	100	9,900	10,000

$$\text{False-Positives} = \frac{990}{1085} = 91\%$$

Positive Predictive Value = 9%

Diagnostic Accuracy = 90%

PREVALENCE OF DISEASE: EFFECT ON POS AND NEG PREDICTIVE VALUE

Prevalence	**50%**	**5%**	**0.5%**	**0.05%**
Sensitivity	90%	90%	90%	90%
Specificity	95%	95%	95%	95%
Pos Pred Value	**94.7%**	**48.6%**	**8.3%**	**0.9%**
Neg Pred Value	**90.5%**	**99.4%**	**99.9%**	**99.99%**
Diagnostic Accuracy	92.5%	94.8%	95%	95%

LYME DISEASE
Clinical Situation

1. Patient with non-specific, vague symptoms not likely to be Lyme disease
   a. Antibody to *B. burgdorferi*: Negative
      Diagnosis: Not Lyme disease
   b. Antibody to *B. burgdorferi*: Positive
      Diagnosis: Not Lyme disease
2. Moral: Don’t order Lyme titers

PRACTICE GUIDELINES FROM THE INFECTIOUS DISEASES SOCIETY OF AMERICA

Published in 2000, 2006 and 2020

1. What's new in 2020
   a. Issued jointly with American Academy of Neurology and the American College of Rheumatology
   b. What is most remarkable is how little has changed
   c. Recommended drugs largely unchanged (doxycycline OK for children of any age for up to 21 days)
   d. Duration of treatment for EM specific (not a range): 10 days for doxycycline, 14 days for amoxicillin and cefuroxime
   e. Recommendation is still to NOT use antimicrobials to treat either post-Lyme disease syndrome or patients with persistent
   f. Symptoms without objective signs of active infection.

LYME DISEASE
Tick Bites

1. Risk of Lyme disease low (1-3%)
2. Risk may be greater from a tick bite that is not recognized
3. Although one dose of doxycycline effective, wide confidence interval around estimate of efficacy
4. Watchful waiting still most reasonable approach
5. If engorged tick (>48 hrs) one dose of doxycycline reasonable (4.4 mg/kg; max 200 mg)

LYME VACCINE

1. An effective vaccine was approved and marketed in 1998
2. Based on the Osp A protein (not expressed in early disease)
3. It is expressed by the bacteria in gut of the tick
4. Antibody-mediated killing of bacteria occurs in the tick
5. Withdrawn by the manufacturer (SKB) because of poor sales and lawsuits that alleged that the vaccine *caused* arthritis
6. New vaccines are being developed (include anitgens of both American and European strains of *B. burgdoferi*)
7. Soon to begin phase 3 clinical trials in the US and in Europe

<u>LYME DISEASE</u>
Nonspecific (Chronic) Symptoms

1. Rarely if ever the *ONLY* manifestation of Lyme disease
   a. Nonspecific (subjective) symptoms accompany *OBJECTIVE* signs of Lyme disease
2. There is no evidence that "chronic Lyme disease" exists and substantial scientific evidence that it does not

(N Engl J Med 2007;357:1422-30)

LYME DISEASE

Post-Treatment Lyme Disease Syndrome

1. Patients who report non-specific symptoms (e.g., fatigue, arthralgia, myalgia, perceived cognitive difficulty, etc) after *documented* Lyme disease
2. If symptoms last ≥6 months and disabling termed post-Lyme disease syndrome (PLDS)
   a. Unclear how common or whether more common after Lyme disease than in general population
   b. Clinical trials of long-term antibiotics in this group:

      Not efficacious; substantial adverse side effects

<u>LYME DISEASE</u>
Advances in Treatment

1. Surgical procedure useful in routine management of patients with Lyme disease

An Internet-ectomy

<u>LYME DISEASE</u>
Alternate Universe

1. There is an alternate universe that we are about to enter in which Lyme disease is something altogether different

“CHRONIC” LYME DISEASE
Definition

1. There is none!! This complicates studies of this entity
2. Definition essentially is that someone (often a “Lyme-literate” doctor) says patient has it
3. Often patients themselves conclude they have chronic Lyme disease and seek provider who will confirm and treat them

“CHRONIC” LYME DISEASE
Definition (ILADS)

“For the purpose of the ILADS guidelines, ‘chronic Lyme disease’ is inclusive of persistent symptomatologies including fatigue, cognitive dysfunction, headaches, sleep disturbance and other neurologic features, such as demyelinating disease, peripheral neuropathy and sometimes motor neurone disease, neuropsychiatric presentations, cardiac presentations including electrical conduction delays and dilated cardiomyopathy and musculoskeletal problems.”

ILADS: International Lyme and Associated Diseases Society

ILADS

Symptoms of Lyme Disease

Fatigue
Low grade fevers, "hot flashes" or chills
Night sweats
Sore throat
Swollen glands
Stiff neck
Migrating arthralgias, stiffness and frank arthritis
Myalgia
Chest pain and palpitations
Abdominal pain, nausea
Diarrhea
Sleep disturbance
Poor concentration and memory loss
Irritability and mood swings
Depression
Back pain
Blurred vision and eye pain
Jaw pain
Testicular/pelvic pain
Tinnitus
Vertigo
Cranial nerve disturbance (facial numbness, pain, tingling, palsy or optic neuritis)
Headaches
Lightheadedness
Dizziness

http://www.ilads.org/lyme_disease/treatment_guidelines_summary.html

Do you have unexplained symptoms? Have you had the following?

If so you could have Lyme Disease. Call your Doctor or Infuserve America for more information at 800/886-9222.

Eye or Vision
Inflammation of the membranes lining eyelids
Inflammation of the eye
Loss or normal pupillary reflexes in response to light
Inflammation of the optic nerve
Abnormal sensitivity to light
Double vision
Inflammation of the iris

Heart
Slowed heart rhythm caused by improper conduction of electrical signals in and to the heart
Inflammation of the heart muscle
Inflammation of the membrane surrounding the heart
Irregular heartbeat
Enlarged heart
Fainting
Dizziness
Shortness of breath
Chest pain, may feel like a heart attack
Rapid heartbeat or skipped beats
A triple cadence in heart sounds, caused by abnormal third or fourth beat

Arthritic
Painful joints
Arthritis: inflamed swollen joints
Aching muscles
Inflammation of tendons
Disease located in the muscles
A collection of fluid that has escaped from a knee joint or a bursa has formed a new sack in an adjacent area

Neuropsychiatric
Mood swings
Irritability
Poor concentration
Emotional instability
Forgetfulness/Memory loss
General mental deterioration
Psychosis
Loss of appetite

Neurologic
Paralysis of a facial nerve
Disease of spinal nerve roots
Meningitis
Inflammation of the brain
Disease of peripheral nerves
Disease of the nerve networks
Spasmodic movements of limbs or facial muscles
Inflammation of multiple nerves
Inflammation of the spinal cord
Loss of muscle coordination caused by disease in the cerebellum of the brain
A type of abnormal increased pressure in brain
Partial paralysis, muscles
Multiple Sclerosis symptoms
Seizures
Inflammation of arteries in the brain
Headache ranging from mild to excruciating
Stiff neck
Impairment of normal sensation
Abnormal sensations such as burning, prickling, or tingling
Sleep Disturbance
Hearing loss
Partial paralysis of one side
Partial paralysis of lower extremities

Other symptoms
Fever, Fatigue, Sore throat
Disease of the lymph nodes
Enlarged spleen, Enlarged liver
Testicular swelling, Nausea
Vomiting, Cough, Hoarseness
Diarrhea, Abdominal cramps

Source:
"Protect Yourself From Lyme Disease."
by Diana Benzola
The World Book Encyclopedia

Call us for more information about a Lyme support group in Colorado at 800/886-9222.

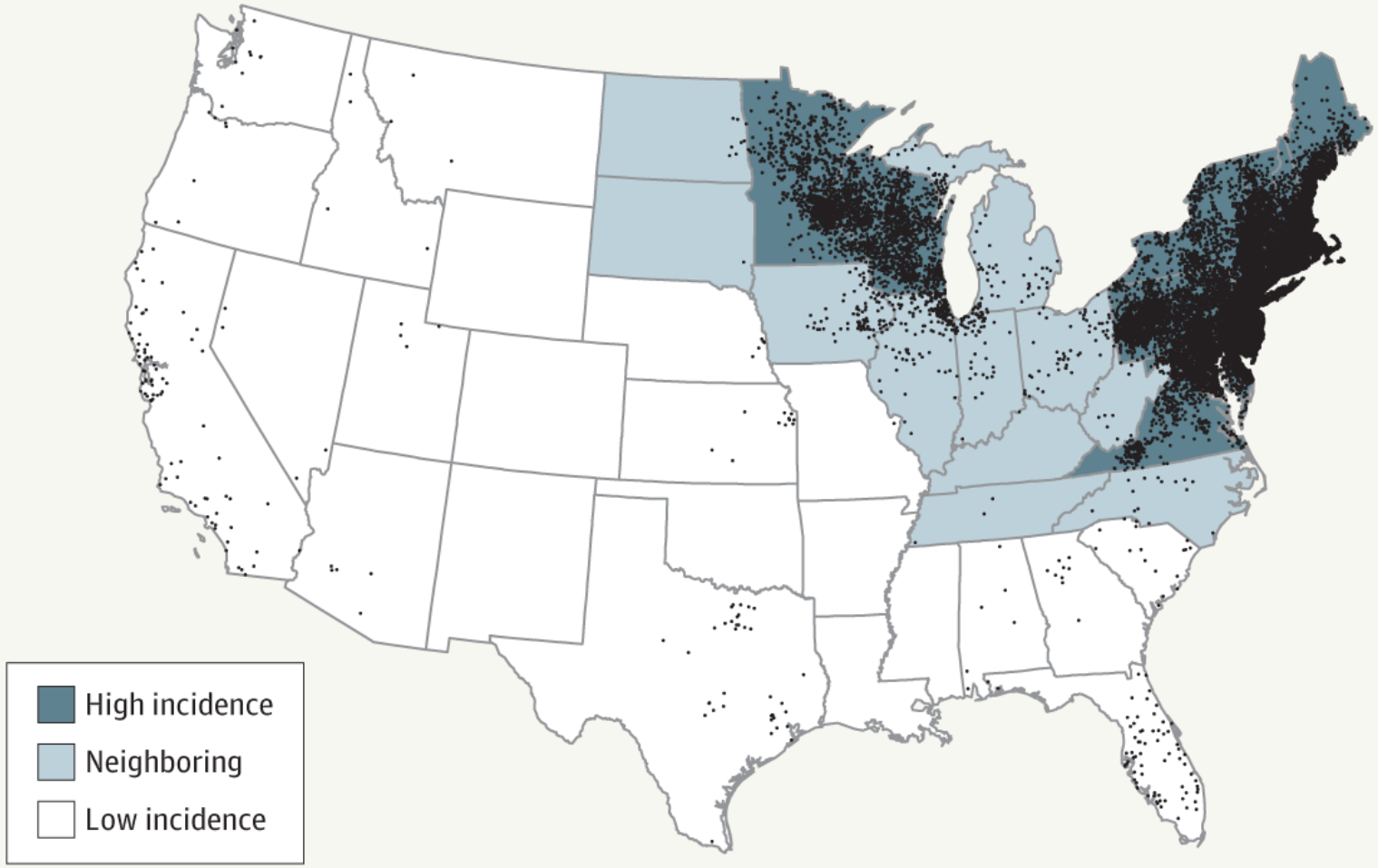
Infuserve America provides cost conscious quality home health care.

“CHRONIC” LYME DISEASE

Key Issue

1. Symptoms vs Signs
2. Persistent symptoms extremely common in the general population
3. Chronic pain—up to 35% of the population
4. Chronic fatigue—10-15% of the population

Average Annual Number of Confirmed Lyme Disease Cases, by County of Residence, United States, 2008–2015[a]



[a]Each dot represents one confirmed case according to county of the patient's residence. State surveillance categories were determined using 3 classifications: high incidence, neighboring, and low incidence. States with an average annual incidence of 10 or more confirmed Lyme disease cases per 100 000 population were classified as high incidence, states that share a border with those states or are located between states with high incidence were classified as neighboring, and all other states were classified as low incidence.

Source: *MMWR Surveill Summ*. 2017;66(22):1-12.

LYME DISEASE SUPPORT GROUPS

http://www.lymenet.org/SupportGroups/

MEDICALLY UNEXPLAINED SYMPTOMS

1. Medically unexplained symptoms (MUS) are physical symptoms with little or no basis to be able to attribute them to an underlying medical disease
2. When an underlying medical condition does exist, symptoms inconsistent with or out of proportion to the illness
3. People with MUS are not necessarily abnormal
4. Many people exhibit MUS but seldom seek care
5. MUS become a problem when lead to frequent healthcare-seeking for feared but nonexistent medical illness

MEDICALLY UNEXPLAINED SYMPTOMS

6. Among patients seeking medical care, prevalence of MUS of any type is in the range of 50 percent, pain being most common
7. For the large majority of patients with mild symptoms, treatment is simple reassurance, symptomatic medications, good provider-patient relationship
8. Laboratory tests should be avoided in these patients with short-term, often stress-related physical symptoms that typically resolve in a week or two
9. More troublesome are the remaining small minority whose symptoms are chronic and more severe, and may result in physical/psychological disability

<u>CHRONIC LYME DISEASE</u>
Medically Unexplained Symptoms

1. Psychosocial factors propel amplification of symptoms
    a. Belief that one has a serious disease
    b. Expectation that one's condition is likely to worsen
    c. “Sick” role
    d. Portrayal of the condition as catastrophic and disabling
2. Patients often strongly assertive; sense of embattled advocacy for their etiologic suppositions
3. Patients often devalue and dismiss medical authority and evidence that conflicts with their beliefs

CHRONIC LYME DISEASE
Medically Unexplained Symptoms

4. Complicated by:
   a. Sensationalized coverage in the media
   b. Internet (chronic Lyme disease: 5 million+ hits)
   c. Profound suspicion of medical expertise and of physicians
   d. Clinical approach that overemphasize biomedical and ignores psychosocial factors

“CHRONIC” LYME DISEASE

Managing the Problem

1. Doctors are part of the problem
2. Good at treating “diseases” (diagnoses); Poor at managing symptoms without a diagnosis
3. Large literature on “medically unexplained symptoms” and “functional somatic syndromes”
4. Saying it is not Lyme disease does not solve the problem
5. Stigma associated with medically unexplained symptoms (“it’s all in your head”)
6. Doctors may have negative feelings about such patients that influence their management

“CHRONIC” LYME DISEASE
Managing the Problem

7. Medically unexplained symptoms are common and should be treated seriously
   a. Patients are experiencing these symptoms and seeking affirmation/sympathy/concern (parents)
8. Explanations should integrate psychological and biological factors and provide patients with a model for managing the problem
9. Associated organic pathology is rare and rarely missed; psychological problems are common and often missed
   a. Depression and/or anxiety often present

“CHRONIC” LYME DISEASE
Managing the Problem

10. Acknowledge Symptoms and Sympathize with the Patient (Parent)
11. Focus on Improving Symptoms
12. It doesn’t matter what the diagnosis is; if Lyme disease, already adequately treated
13. If some other serious medical condition, would already have become apparent
14. Exercise, counseling, improve sleep
15. Avoid additional diagnostic tests if at all possible

“CHRONIC” LYME DISEASE
Managing the Problem

16. Paradigm for many other functional syndromes
17. Focus on symptoms, not diagnosis
    a. Trusting relationship important
    b. Exercise, counseling, improve sleep, in some instances medications (e.g., antidepressant)
    c. Get patients back to work, school, up and going
18. Primary care docs need to be trained how to manage patients with MUS who do not need to be referred

PROGRAM FOR CHILDREN WITH ANXIETY/MUS

1. Study about to start
2. Happy for referrals from community practices
3. Led by folks from the Anxiety Program at the Child Study Center
4. Conducted on zoom in the evenings
5. Program for parents of these children
6. Turns out that get parents to set limits and to not accommodate their child's anxiety, as effective as cognitive behavioral therapy

THANK YOU!!