Lyme Disease

Grand Rounds
July 5 2016
Adam Clements DO

Disclosures

- I have no conflicts of interest to report

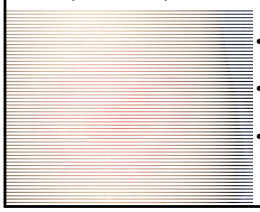
Important note (irritated rant)

- All of my information for this talk will be based on the current standard of care and IDSA guidelines
- Many other opinions exist and a separate organization called the ILADS, the International Lyme and associated diseases society
- Their "expert opinion" statements differ from the standard of care, prioritize patient preference over objective data, and use outcome measures which are irrelevant to population health and guideline formation.

If you have any questions or concerns about the differences between ILADS and IDSA I will answer them at the end or later on after this talk. Otherwise I'll not be covering ILADS "guidelines" or "data" today

Case Study

Above: Day 12 Below: Day 14



- 30 YO male presents with this rash 12 days after a tick exposure. No implanted ticks found
- Symptoms started on day 8 with headache which progressed to fevers, myalgia, a swollen elbow and sore joints.
- No significant PMH or PSH
- No known allergies
- Vitals BP 110/70, P 70, T 102 (temporal)

Which of the following is most appropriate

A. Treat with 21 days of doxycycline
B. Check Lyme serology
C. Observation
D. Check Lyme serology, a Tick panel, and treat with 21 days of doxycycline

A. Treat with 21 days of doxycycline
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Presumptive treatment is appropriate. The sensitivity of physical exam is better than that of the test within the first month. Patient has not had enough time to mount an antibody response

Your patient doesn't get better, he develops a high fever, low blood pressure, worsening fatigue, jaundice and tachycardia. Which is most likely to be helpful ?

A. An additional 3 weeks of doxycycline with consideration of a 2 month course for treatment failure
B. Atovaquone and azithromycin
C. IV ceftriaxone
D. Clindamycin and quinine

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If you see this patient in your clinic its probably appropriate to admit them. Babesiosis can be severe and life threatening. Unlike Lyme which is almost never fatal

This patient likely has Babesiosis which is a common coinfection with Lyme. Either B or D would be effective. B is first line. D is second line. Anaplasma and Ehrlichia are both effectively treated with doxycycline alone.

A and C would be completely ineffective
The diagnosis is made by smear (fast) or serology (slow)

Common misconceptions

1. Serologic testing for Lyme is unreliable and the diagnosis should be made clinically
2. Seropositivity following treatment indicates treatment failure
3. Lyme is often fatal without treatment
4. Fatigue and memory disorders following infection are evidence of Lyme encephalitis
5. If symptoms persist after treatment prolonged antibiotic courses are needed.
6. Improvements in symptoms following treatment proves the diagnosis despite negative serology
7. Erythema migrans rashes always have a central clearing

How big of a problem is Lyme?

- Most common vector borne illness in the US
- 95% of cases from 13 states
- In Maine, it's the 3rd most common bacterial infection
- Incidence is increasing
- Numerous misconceptions and controversies exist and circulate in popular culture

Prices at AWH

Lyme antibody screen: $131
Lyme western blot: $274

Doxycycline: $30-60

Tick ID: $66

Tick Panel PCR: $364

$405 in lab costs alone for one positive screen. $131 for each negative screen not including the cost of the tick panel which is often ordered when Lyme is suspected.

Tick panel testing from AWH reference lab

April 2013-March 2014

Tick PCR Panel*	
Orders	1316
Positive (1 or more organisms)	47
ANAPLASMA	
BABESIA MICROTI	
EHRLICHIA CHAFFEENSIS	
EHRLICHIA EWINGII/CANIS	
EHRLICHIA MURIS-LIKE	

3.6% positive

June 2015 - May 2016

Tick Borne Panel by PCR (does not include Lyme)	
Total Orders	1590
Anaplasma phagocytophilum	50
Babesia microti	8
Ehrlichia chaffeensis	0
Ehrlichia ewingii	0
Ehrlichia muris-like (EML)	1

3.7% positive

No improvement….
$1,019,200 spent on negative tests

Lyme screening from AWH reference lab

June 2015 - May 2016

Lyme IgG & IgM Screen	
Total Orders	3688
Negative	3340
Positive	334
Equivocal	164

14% positive or equivocal

Lyme IgG & IgM Screening	
Total Orders	3228
Negative	2962
Positive	237
Equivocal	29

9% positive or equivocal

We got worse!
391,362$ on negative screening. Doesn't include the confirmatory testing cost (some of those negative as well)

Take home points…

We spend a lot of money on testing, we could do better.

We need to work on our pre-test probability

My lecture last time didn't help!

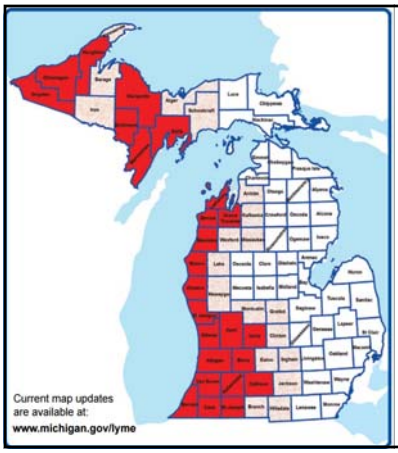
I'll try harder this time

Lyme incidence by county in 2015

Cases/100000 residents

County	Confirmed	Total
Marathon (AWH)	49.34	52.29
Lincoln	80.72	129.86
Wood (Riverview)	58.42	59.78
Langlade (Antigo)	36.06	72.13
Oneida (Rhinelander clinic)	75.9	132.16
Taylor (Medford)	58.2	58.2
Portage (St Point clinic)	56.75	100.73
Vilas (land o lakes clinic)	51.4	70.1
Shawano (several)	36	60
Washburn	248	350

In 2015 there were a total of 193 total cases of Lyme in the UP. No county breakdown available However they state the problem is severely under-reported



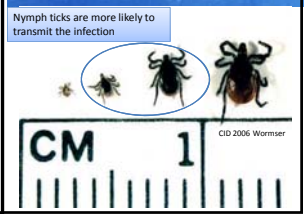
Counties in Michigan with proven or suspected lyme as of 2015

Red: proven in a patient

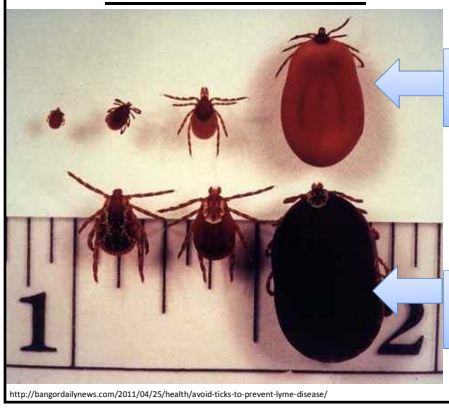
Pink: found in a tick

Etiology

- Borrelia species
  - Different species depending on the region
  - Typically known as the "blacklegged" or "deer" tick
  - *B. Burgdorferi* in north America
  - *B garinii* and *B afzelii* in Europe
- Ixodes ticks
  - Different species of borrelia tend to be transmitted by different ticks.
  - Ticks may be active any time the temperature rises above 40F



Tick identification



Ixodes ticks at various lifecycle stages

Dermacentor ticks at various lifecycle stages

http://bangordailynews.com/2011/04/25/health/avoid-ticks-to-prevent-lyme-disease/

A farmer presents to your office with an imbedded, non-engorged Ixodes tick. What is the most evidence based next step?

A) Remove the tick, treat with a full 10 day course of doxycycline or amoxicillin
B) Leave the tick attached and let it fall off on its own
C) Remove the tick, give prophylactic doxycycline
D) Remove the tick, provide reassurance that the chance of infection is low

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In a recent study using infected ticks what percentage imbedded for less than 72 hours caused an active infection in the host?

A: 0%
B: 10%
C: 20%
D. 30%
E. 40%

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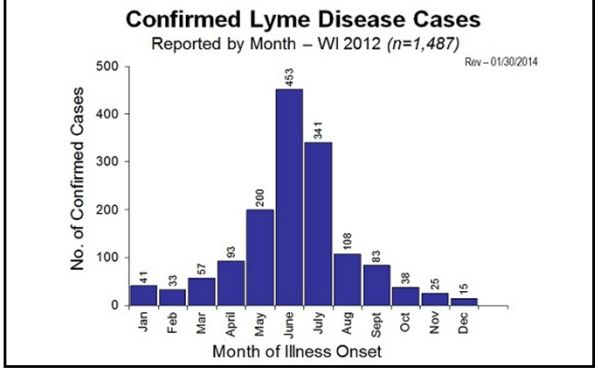
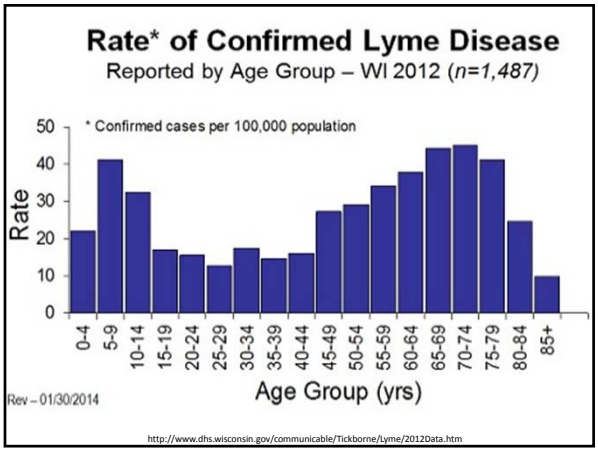
C: 20%
D. 30%
E. 40%

The shortest imbedded time to documented infection is 36 hours for nymphs and 48 hours for adults. Infection rates for any tick bite less than 72 hours is estimated to be about 1-2%

"The seasonal and geographic distribution of cases and the association with a skin lesion suggest that a virus carried by a biting insect may be responsible…."





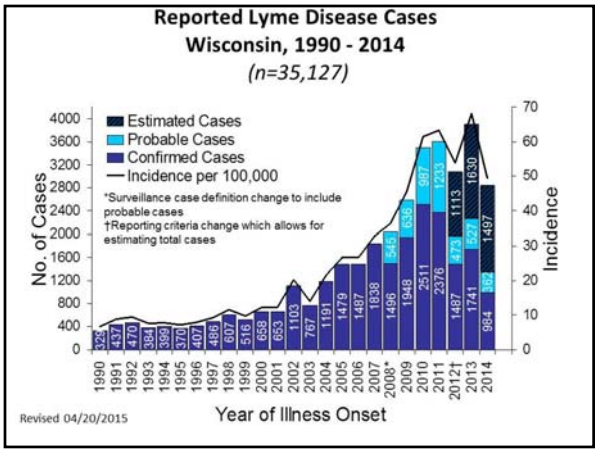
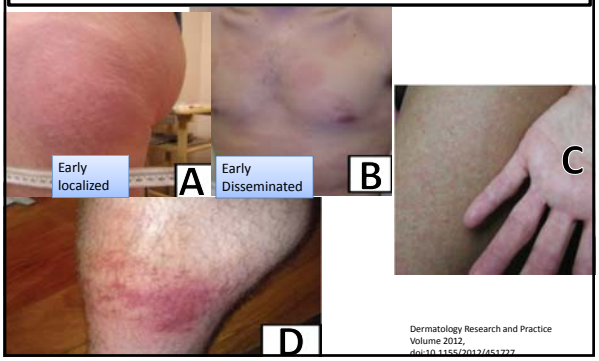


Photo quiz: Which of the following rashes is suggestive of early Lyme infection?



Dermatology Research and Practice Volume 2012, doi:10.1155/2012/451727

Early Localized Disease

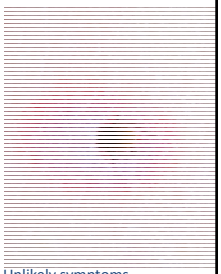
Characteristic rash

80% of seropositive patients
Within one month but usually within 7-14 days of tick exposure.
1/3 will have central clearing,
Confluence, ulceration and necrosis may occur.

Constitutional symptoms

Fatigue 54%
Anorexia 25%
Headache 42%
Neck Stiffness 35%
Myalgias 44%
Arthralgia 44%
Regional lymphadenopathy 23%
Fever 16%

Steere et al, AJM jan 2003



Unlikely symptoms
Respiratory or GI -
The presence of any of these should prompt workup for an alternative diagnosis

Early Disseminated Disease

- One study from 1983 found that half of all untreated patients with known Lyme developed multiple EM lesions.
- 16% of patients with previously unknown Lyme developed multiple lesions
- Multiple EM lesions are from hematogenous or lymphatic spread of bacteria, not multiple tick bites
- Neurologic symptoms may occur but are rare
- Death following disseminated disease doesn't occur without heart or brain involvement

Steere et al, Ann Intern Med 1983;99(1):76-82
Wormser et al Clin infect dis. 2006;43(9):1089 www.uptodate.com

Neurologic symptoms associated with early disseminated Lyme

- Cranial nerve palsies (typically facial nerve)
  - Bells palsy is the most common neurologic manifestation,
  - 90% spontaneously resolve
  - Most common cause of acute bells palsy in children
  - Bilateral bells palsy is nearly pathognomonic for Lyme
- Peripheral neuropathy
- encephalitis

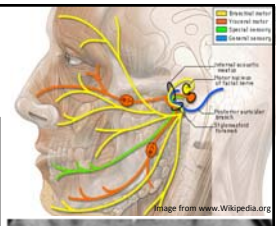


Image from www.Wikipedia.org

AJNR 30:1079 – 87 Jun-Jul 2009

Lyme Arthritis

- Up to 60% of untreated patients following documented erythema migrans will develop joint involvement ranging from mild arthralgia to a septic joint
- Left untreated 20% of cases resolve per year
- ≤10% of patients will have ongoing joint pain after treatment

http://www.cdc.gov/lyme/signs_symptoms/

Lyme Arthritis

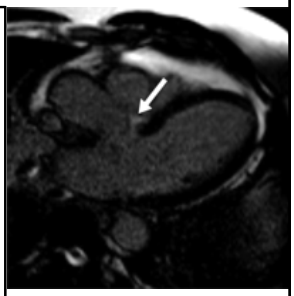
- Mild cases typically include migratory or isolated arthralgia, knee is most common.
- When an effusion is present it will always recur if tapped
- ELISA on peripheral blood or PCR of joint aspirate on patients with septic joints both have high sensitivity and nearly 100% positive predictive value
- Death attributed to Lyme arthritis hasn't been reported in the literature

What are the recommended criteria for diagnosing Lyme Carditis?

- **A** Echocardiogram showing vegetations with new Lyme diagnosis
- **B** New Lyme diagnosis and new AV block
- **C** Gadolinium enhancement on cardiac MRI
- **D** Myocardial infarction associated with new Lyme infection

Lyme Carditis

- <10% of untreated patients will have cardiac involvement
- Usually includes focal carditis involving the AV node
- Patients will present with AV block, usually high grade
- Treatment with antibiotics usually leads to complete resolution
- Advanced imaging is rarely if ever needed, diagnosis is based on positive lyme serology and new AV block



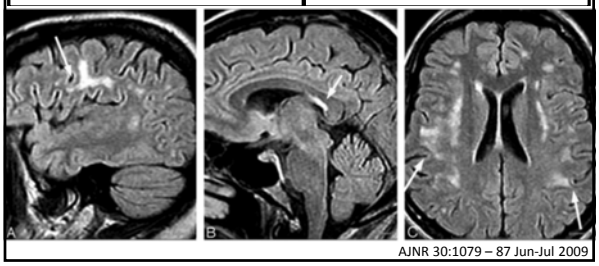
Cardiac MRI imaging showing Gadolinium enhancement of the inferior anteroseptal wall in Lyme myocarditis

Circulation 2008; 118:1881-1884

Lyme Meningitis

- Rare, even in endemic areas .1-1% of confirmed Lyme cases
- CSF and MRI are both typically positive
- Most cases reported in Europe

- Patients have clinical signs of meningitis and Lyme
- IV ceftriaxone is the preferred treatment but doxycycline appears to be as effective



AJNR 30:1079 – 87 Jun-Jul 2009

Lyme Encephalopathy

- Altered CNS function without parenchymal infection in the setting of disseminated Lyme
- Related to toxic, metabolic and immune factors
- Imaging will not show any objective abnormalities
- Antibiotic treatment should rapidly resolve symptoms in most patients
- CSF culture and imaging are negative

Up to 30% of patients following treatment for Lyme report ongoing symptoms, what is the most likely cause?

A. Treatment failure due to bacterial resistance
B. Chronic Lyme
C. Heightened awareness of unrelated symptoms
D. Incorrect diagnosis, they never had Lyme

Post treatment Lyme Disease Syndrome

- The presence of any widespread musculoskeletal pain, cognitive complaints, radicular pain, paresthesia or dysesthesia interfering with function within 6 months of infection and persist for at least 6 months
- Symptoms typically begin soon after treatment and typically improve and/or resolve over time
- Often referred to as "chronic Lyme" and is commonly thought to reflect ongoing infection
- Up to 30 % of treated patients complain of ongoing symptoms
- Prospective placebo controlled trials show that 30% of PTLDS patients treated with placebo or doxycycline will report symptomatic improvement. No benefit of antibiotics were found. Side effects and adverse events were common in the doxycycline group

NEJM 370;18 May 1, 2014
Clinical Infectious Diseases 2014;58(9):1267–72

Table 5. Symptoms and Difficulties With Activities Among Patients and Age-Matched Controls Without Lyme Disease*

	Patients (n = 212)	Controls (n = 212)	Relative Risk (95% CI)	*P* Value
Reported Increases in Symptoms, %				
Swollen joints	18.9	14.2	1.33 (0.86-2.06)	.24
Numbness	19.8	18.9	1.05 (0.71-1.55)	.90
Headaches	17.0	17.9	0.95 (0.63-1.43)	.90
Memory problems	18.0	14.6	1.23 (0.79-1.80)	.43
Joint or muscle pain	33.5	24.1	1.39 (1.03-1.89)	.04
Neck pain	13.7	15.1	0.91 (0.57-1.44)	.78
Fatigue	19.3	14.6	1.32 (0.86-2.02)	.24
Reported Increases in Difficulties With Normal Daily Activities, No. (%)†				
Attending school or work	7/179 (3.9)	12/168 (7.1)	0.55 (0.22-1.36)	.24
Housework	23/178 (12.9)	24/188 (12.8)	1.01 (0.59-1.73)	.99
Exercise	31/212 (14.6)	24/212 (11.3)	1.24 (0.76-2.03)	.47
Sleeping	40/212 (18.9)	44/212 (20.8)	0.91 (0.62-1.33)	.71
Falling asleep	18/212 (8.5)	27/212 (12.7)	0.67 (0.38-1.17)	.21
Naming objects	38/212 (17.9)	30/210 (14.3)	1.25 (0.81-1.95)	.35
Word finding	46/212 (21.7)	51/210 (24.3)	0.89 (0.63-1.27)	.56
Judgment	9/211 (4.3)	3/211 (1.4)	3.00 (0.82-10.93)	.14
Appetite	10/212 (4.7)	11/212 (5.2)	0.91 (0.39-2.10)	.85
Ability formulating ideas	24/212 (11.3)	8/209 (3.8)	2.96 (1.36-6.43)	.01
Attending gym class	4/56 (7.1)	6/50 (12.0)	0.60 (0.18-1.99)	.50

*CI indicates confidence interval.
†Denominators differ because not all activities applied to all subjects (eg, not all subjects did housework).

PTLDS management

- Additional antibiotics have potential for harm and are no more beneficial than placebo
- Additional testing for Lyme will likely be positive due to persistence of circulating immunoglobulin, this doesn't reflect treatment failure
- Supportive care, frequent follow-up reassurance, and workup for other etiologies is recommended

Which of the following should be screened for possible Lyme ?

A: 65 YO male with a 7cm confluent, pink, oval rash on his leg after bird hunting 5 days ago

B: 12 YO from Edgar with increasing polyarthralgia, headache, and fatigue

C: 50 YO with headache and difficulty doing normal tasks after being treated for Lyme 3 months ago

D: 45 YO who found an imbedded tick yesterday and brought it with him today, 3cm red rash around an obvious bite wound

Which of the following should be screened for possible Lyme ?

A: 65 YO male with a 7cm confluent, pink, oval rash on his leg after bird hunting 5 days ago

don't test, treat

B: 12 YO from Edgar with increasing polyarthralgia, headache, and fatigue

test, don't treat

C: 50 YO with headache and difficulty doing normal tasks after being treated for Lyme 3 months ago

supportive care

D: 45 YO who found an imbedded tick yesterday and brought it with him today, 3cm red rash around an obvious bite wound

lesion too small. Criteria 5cm

Who should get ELISA screening?

TABLE

Pretest probability scenarios for suspected Lyme disease

CLINICAL SCENARIO	TEST?	RATIONALE
Erythema migrans	No	Pretest probability high; clinical diagnosis of Lyme disease (treat without testing)
Signs/symptoms of disseminated Lyme disease, live in endemic region	Yes	Pretest probability intermediate; high prevalence yields high PPV
Signs/symptoms of disseminated Lyme disease, live in non-endemic region	Yes	Pretest probability intermediate; cost-effective
Nonspecific myalgias	No	Pretest probability too low
Asymptomatic patient	No	Pretest probability too low
Empiric antibiotic response; treatment	No	Antibiotic treatment decreases humoral testing not cost effective
Test-of-cure	No	Test remains positive after treatment
Immunized	No	ELISA will be positive (Western blot could assess exposure)

The Journal Of Family Practice VOL 54, NO 12 / DECEMBER 2005

Recommended testing algorithm

Intermediate pretest probability

↓

Sensitive IGM /IGG antibody screening using ELISA

↓

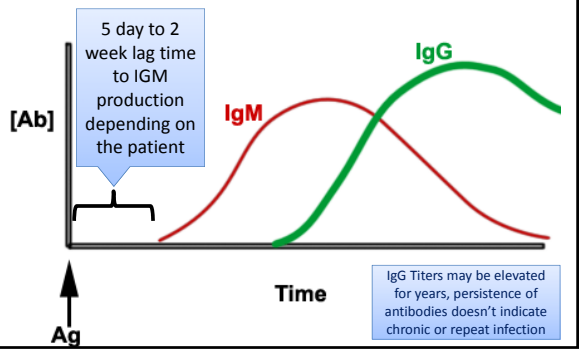
Specific Lyme testing using western blot to IGM and IGG

55 YO with a history of Erythema migrans treated with doxycline 1 year ago. He presents with body aches and a fever. He had an imbedded and engorged tick 6 weeks ago. No rash. Western blot shows IgM bands but no IgG band. You should:

A. Treat with 21 days of doxycycline
B. Observe
C. Refer to Dr Bowler
D. Obtain a Lyme PCR on peripheral blood

A. Treat with 21 days of doxycycline
   After 4 weeks IgG must be positive for the test to be considered positive
B. Observe
C. Refer to Dr Bowler
   He probably doesn't need to see them, you can handle it
D. Obtain a Lyme PCR on peripheral blood
   Very low sensitivity in peripheral blood this long into the infection. Sprochetemia is short lived
   If you had a different fluid to test (joint fluid or CSF) the sensitivity would be near 100%

Antibody response following infection



IgM vs IgG

IgM

- Made early, always detectable by 2 weeks post exposure but as early as 5 days.
- Not T Cell dependent so no memory t cells. No long lasting Igm titers
- Wanes over a period of months regardless of treatment
- Useful to look at early in the disease process. After 4-6 weeks it shouldn't be relied upon to diagnose or rule out infection

IgG

- Made later, maybe
- Assuming they weren't treated right away which will reduce antigen presentation to CD4 cells, no memory cells, no long lasting titers. Maybe no IgG titer at all
- Titers may be elevated for up to a few years post-exposure
- Protective antibody response???

Testing patients with an EM rash isn't sensitive due to lack of seroconversion

Table ... Two-Tier Serology Using ... sorbent Assay and Western ... ndemic Area

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Early localized				
Acute phase	17	98	75	26
Convalescent phase	53	98	90	83
Early disseminated				
Cardiac or neurologic manifestations	100	98	87	100
Multiple erythema migrans lesions	43	98	89	79
Late				
Arthritis or neurologic manifestations	100	98	94	100

AAFP June 1, 2012 Volume 85, Number 11

Sensitivity/specificity of PCR

Clinical specimen and region	No. of studies included	Median % sensitivity[b] (range)	Reported % specificity range
Skin biopsy			
EM	16	69 (36–88)	98–100
United States	4	64 (59–67)	98–100
Europe	12	73 (36–88)	100
ACA, Europe	8	76 (54–100)	100
Blood, plasma, serum	6	14 (0–100)	
United States	3	18 (0–59)	100
Europe	3	10 (4–100)	NA[c]
CSF	16	38 (12–100)	93–100
United States	6	73 (25–93)	93–100
Europe	10	23 (12–100)	98–100
Synovial fluid	8	78 (42–100)	100
United States	4	83 (76–100)	100
Europe	4	66 (42–85)	100

Aguero-Rosenfeld Et Al. Clinical Microbiology Reviews, July 2005, p. 484–509

Are non-specific labs helpful?

Non-specific labs can't rule in or out Lyme and are not particularly useful and likely shouldn't be ordered in the absence of another indication.

Frequency of elevated labs:

- ESR: 24%
- CPK: 12%
- Leukocytosis: 5%
- Leukopenia: 5%
- Anemia: 3%
- Thrombocytopenia: 1.5%
- AST/ALT: 37%

Patients with Anaplasma will have leukopenia, thrombocytopenia and elevations in their AST and ALT. These should be checked if there is a clinical suspicion of Anaplasma, erlichia or babesia along with a peripheral smear and consideration for a tick panel

Treatment of Early localized, arthritis*, or uncomplicated disseminated Lyme

Shapiro. NEJM 370;18 May 1, 2014

Drug	Dose	Duration	Comment
Doxycycline	200mg/day 4mg/kg/day	14-21 days (10 is adequate for EM only)	Do not use in children <8 or pregnant women
Amoxicillin	1500mg/day 50mg/kg/day	14-21 days	Ineffective vs anaplasma and babesia which can be transmitted with Lyme in WI
Cefuroxime	1000mg 30mg/kg/day	14-21 days	Ineffective vs anaplasma and babesia which can be transmitted with Lyme in WI
*Arthritis	For acute Lyme arthritis 28 days of treatment is required, most experts recommend retreatment with a second 28 day course		

Treatment of meningitis* or carditis

Drug	Dose	Duration
Ceftriaxone	2g/day 50-75mg/kg/day	10-28 days
Cefotaxime	6g/day 150mg/kg/day	10-28 days

* There is evidence form Europe that treatment of meningitis with doxycycline orally is as good as IV treatment. US trials haven't been done however and the species of Borrelia is different in europe. Doxycycline does penetrate well into the CNS

Shapiro. NEJM 370;18 May 1, 2014

Lyme prophylaxis

- Due to low incidence of infection following tick bites even in ticks which carry the bacteria routine prophylaxis isn't recommended following tick bites.
- Prophylaxis with 200mg of doxycycline for one dose has been shown effective in preventing infection in adults. Amoxicillin has not proven effective as prophylaxis.
- NNT for Doxy in endemic areas is 40 following a tick embedded for less than 72 hours.

Antibiotic prophylaxis should be used only in patients who meet ALL of the following criteria*:
Attached tick identified as an adult or nymphal Ixodes scapularis tick (deer tick)
Tick is estimated to have been attached for ≥36 hours (by degree of engorgement or time of exposure)
Prophylaxis is begun within 72 hours of tick removal
Local rate of infection of ticks with B. burgdorferi is ≥20 percent (these rates of infection have been shown to occur in parts of New England, parts of the mid-Atlantic States, and parts of Minnesota and Wisconsin)
Doxycycline is not contraindicated (ie, the patient is not <8 years of age, pregnant, or lactating)

Wormser, GP, Dattwyler, RJ, Shapiro, ED, et al. The Clinical Assessment, Treatment, and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesiosis: Clinical Practice Guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2006; 43:1089.

Preventing Lyme

- Avoid tick bites by covering exposed skin, checking after possible exposure, or using repellants
- Repellants: permetherin and DEET have the best data
- Pesticides: carbaryl, cyfluthrin, deltamethrin
- Check yourself and your dog, bathe after possible exposure.

Common misconceptions

1. Serologic testing for Lyme is unreliable and the diagnosis should be made clinically
   Sometimes, depends on pretest probability
2. Seropositivity following treatment indicates treatment failure
   Circulating IGM and IGG remain after treatment, repeat testing not indicated
3. Lyme is often fatal without treatment
   Generally with carditis or encephalitis which are both rare
4. Fatigue and memory disorders following infection are evidence of Lyme encephalitis
   Symptoms are most likely unrelated to Infection, testing will be negative
5. If symptoms persist after treatment prolonged antibiotic courses are needed.
   Potentially harmful, no better than placebo
6. Improvements in symptoms following treatment proves the diagnosis despite negative serology
   Rarely, 1/3 patients with non-specific symptoms improve when treated with placebo. When testing is used appropriately it is sensitive and specific.
7. Erythema migrans rashes always have a central clearing
   Only 1/3 of the time, lesions may be ulcerated and/or confluent

A 35 YOWF is seen in the walk-in clinic with complaints of a 5 month history of fatigue, intermittent arthralgia, proximal myalgias, headache, and low-grade temperatures not exceeding 100°. Her temperature is 99.6°. Exam is otherwise unremarkable. Laboratory studies show: CBC- WNL, ESR 24, comprehensive panel WNL, Lyme EIA 1.26/IgM WB (+)/IgG WB (-). The most appropriate therapeutic intervention is:

A. Start ceftriaxone for late Lyme disease.
B. Start doxycycline for late Lyme disease.
C. Provide reassurance and symptomatic care.
D. Admit to hospitalists for sepsis

The patient is given a four week course of doxycycline 100 mg b.i.d. She returns to her PCP two months later with the same symptoms. She reports that her symptoms improved on doxycycline, but then worsen again after completing the four week course. Lyme serology is repeated with EIA 1.35/ IgM WB (+)/IgG WB (-). You would now:

A. Give four weeks of ceftriaxone for chronic Lyme disease.
B. Provide reassurance and symptomatic care.
C. Give another four week course of doxycycline for chronic Lyme disease.
D. Refer for ID consult.

Closing thoughts from Dr Bowler

- Lyme serology is frequently negative at the time of initial presentation, and should not dissuade from treating for Lyme disease in the right clinical setting (even in the absence of ECM). In the absence of ECM, a repeat ("convalescent") serology two weeks later will be positive if the syndrome is due to Lyme disease.
- ECM is virtually pathognomonic for acute Lyme disease, and serologic testing is generally not necessary.
- Prompt treatment of early Lyme disease is nearly always (95%) curative, and prevents chronic sequelae.
- Chronic somatic symptoms that arise after delayed treatment of Lyme disease are immunologic in nature, and repeated courses of antibiotics should not be given.
- Once positive, Lyme serology (EIA and IgG WB) will remain positive for years (indefinitely ?), and does not indicate chronic infection.
- In the presence of chronic symptoms of greater than one months duration, an IgM WB should not be obtained, or if it is, the results disregarded.
  - A negative IgG WB excludes Lyme disease as the cause chronic symptoms.
- In serologically or clinically (ECM) confirmed Lyme disease, a positive IgM WB can persist for $\geq$ 12 months and does not, in and of itself, indicate persistent, or new Lyme infection.
- Be alert to the possibility of co-infection with Anaplasma or Babesia.
  - The "footprint" of Anaplasma is: leukopenia, thrombocytopenia, and elevated liver function tests.
  - Non-response to doxycycline could suggest Babesiosis (dx = peripheral smear or PCR).
  - A syndrome of "chronic anaplasmosis" does not exist.
- The disease is "Lyme", not "Lymes"!!