Lyme Disease
Diagnostic Challenges and Clinical Controversies

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Disclosures

- No financial disclosures
Objectives

- Review and apply current guidelines used to diagnose and treat Lyme disease
- Identify the limitations of laboratory tests used for the diagnosis of Lyme disease
- Debate the clinical controversies associated to Lyme disease
In the US Lyme disease is caused by the bacteria *Borrelia burgdorferi* sensu stricto and is transmitted to humans through the bite of infected blacklegged ticks.
The first case of Lyme disease in the United States was described by dermatologist Rudolph J. Scrimenti in 1970.
A cluster of cases originally thought to be juvenile rheumatoid arthritis was identified in southeastern Connecticut affecting the towns of Lyme, Old Lyme and East Haddam.
Willy Burgdorfer isolated the spirochetes in 1982
Cases by Year

- Most commonly reported tick-borne illness in North America
Reported Cases of Lyme Disease—United States, 2014

One dot is placed randomly within the county of residence for each confirmed case. Though Lyme disease cases have been reported in nearly every state, cases are reported based on the county of residence, not necessarily the county of infection.

1 dot placed randomly within county of residence for each confirmed case
2 year life cycle

Eggs → Nymph → Eggs → Larva → Adults → Eggs

Spring: Risk of human infection greatest in late spring and summer

Winter: Winter

Fall: Fall

Summer: Summer

CDC
Risk of infection and duration of tick attachment

- In the US the risk of infection after the bite of an infected tick is approximately 1 - 3%

- The risk of infection is minimal if ticks stay attached for less than 72 hours

- Doxycycline 200 mg single dose is an effective prophylaxis regimen

Duration of tick attachment as a predictor of the risk of Lyme disease in an area in which Lyme disease is endemic. J Infect Dis 1997;175:996e9.

Risk of infection and duration of tick attachment

1. The attached tick adult or nymphal *L. scapularis* tick that is estimated to have been attached for 36 hours

2. Prophylaxis can be started within 72 hours of the time that the tick was removed

3. Local rate of infection of these ticks with *B. burgdorferi* is 20%

4. Doxycycline treatment is not contraindicated

Risk of infection and duration of tick attachment

Cases by Symptoms

- Cardiac: 1%
- Meningitis/Encephalitis: 1%
- Radiculoneuropathy: 4%
- Bell's palsy: 9%
- Arthritis: 31%
- Erythema migrans: 70%

N = 154,405

Number of cases
Clinical manifestations of Lyme disease

Early localized disease - days to one month after the tick bite

- Erythema migrans - 80% of patients
  - Fatigue
  - Malaise
  - Lethargy
  - Mild headache
  - Mild neck stiffness
  - Myalgias
  - Arthralgias
  - Regional lymphadenopathy
Clinical manifestations of Lyme disease

Early disseminated disease - weeks to months after the tick bite

- Carditis - 1% reported cases
  - AV nodal block
  - Mild cardiomyopathy
  - Myopericarditis
Clinical manifestations of Lyme disease

Early disseminated disease - weeks to months after the tick bite

- Neurologic disease - 15% of untreated patients
  - Lymphocytic meningitis
  - Cranial neuropathy
  - Peripheral neuropathy
  - Myelitis or encephalitis
Clinical manifestations of Lyme disease

**Early disseminated disease** - weeks to months after the tick bite

- Musculoskeletal involvement - 60% of untreated patients
  - Migratory arthralgias
Clinical manifestations of Lyme disease

**Early disseminated disease** - weeks to months after the tick bite

- **Skin involvement**
  - Multiple erythema migrans lesions
  - Borrelial lymphocytoma (in Europe)

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en.wikipedia.org
Clinical manifestations of Lyme disease

Late or chronic disease - occurring months to years after the tick bite

- Musculoskeletal symptoms - approximately 60% of untreated patients
  - Intermittent monoarticular or oligoarticular arthritis

- Neurologic disease - incidence has not been established
  - Peripheral neuropathy or encephalomyelitis
Clinical manifestations of Lyme disease

Late or chronic disease - occurring months to years after the tick bite

- Cutaneous involvement
  - Acrodermatitis chronica atrophicans (described only in Europe)
The Clinical Assessment, Treatment, and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesiosis: Clinical Practice Guidelines by the Infectious Diseases Society of America


Evidence-based guidelines for the management of patients with Lyme disease, human granulocytic anaplasmosis (formerly known as human granulocytic ehrlichiosis), and babesiosis were prepared by an expert panel of the Infectious Diseases Society of America. These guidelines replace the previous treatment guidelines published in 2000 (Clin Infect Dis 2000; 31 [Suppl 1]:1–14). The guidelines are intended for use by health care providers who care for patients who either have these infections or may be at risk for them. For each of these tick-borne infections, information is provided about prevention, epidemiology, clinical manifestations, diagnosis, and treatment. Tables list the doses and durations of antimicrobial therapy recommended for treatment and prevention of Lyme disease and provide a partial list of therapies to be avoided. A definition of post-Lyme disease syndrome is proposed.

EXECUTIVE SUMMARY

Background

Lyme disease is the most common tickborne infection in both North America and Europe. In the United States, Lyme disease is caused by *Borrelia burgdorferi*, which is transmitted by the bite of the tick species *Ixodes scapularis* and *I. pacificus*. Clinical manifestations most often involve the skin, joints, nervous system, and heart. Extracutaneous manifestations are less commonly seen than in earlier years. Early extracutaneous infection with *B. burgdorferi* is called erythema migrans, which is the most common clinical manifestation of Lyme disease. *I. scapularis* may also be infected with and transmit *Anaplasma phagocytophilum* (previously referred to as *Ehrlichia phagocytophila* and/or *Babesia microti*), the primary cause of human granulocytic anaplasmosis. Infection with I. scapularis tick may lead to the development of Lyme disease, human granulocytic anaplasmosis (HGA, formerly known as human granulocytic ehrlichiosis), or babesiosis as a single infection or, less frequently, as a combination. Clinical findings are sufficient...
### Controversy # 1 - Treatment Recommendations IDSA and EUCALB

**Table 4**

Treatment recommendations by the IDSA and EUCALB (In the daily dose recommendations by EUCALB, “same” indicates that the same dose as recommended by the IDSA).

<table>
<thead>
<tr>
<th>Condition</th>
<th>Compound</th>
<th>Route</th>
<th>Adults (A), children (C)</th>
<th>IDSA</th>
<th>EUCALB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Daily dose</td>
<td>Duration (in days)</td>
</tr>
<tr>
<td>EM, BL</td>
<td>Doxycycline</td>
<td>Oral</td>
<td>A</td>
<td>2 × 100 mg</td>
<td>14 (10–21)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C</td>
<td>2 × 2 mg/kg</td>
<td>Same</td>
</tr>
<tr>
<td></td>
<td>Amoxicillin</td>
<td>Oral</td>
<td>A</td>
<td>3 × 500 mg</td>
<td>14 (14–21)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C</td>
<td>3 × 500 mg</td>
<td>Same</td>
</tr>
<tr>
<td></td>
<td>Cefuroxime axetil</td>
<td>Oral</td>
<td>A</td>
<td>2 × 500 mg</td>
<td>14 (14–21)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C</td>
<td>20 mg/kg</td>
<td>1 × 500 mg</td>
</tr>
<tr>
<td></td>
<td>Penicillin V</td>
<td>Oral</td>
<td>A</td>
<td>3 × 500 mg</td>
<td>14 (10–21)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C</td>
<td>3 × 500 mg</td>
<td>1 × 500 mg</td>
</tr>
<tr>
<td></td>
<td>Azithromycin – not recommended as first line therapy(a)</td>
<td>Oral</td>
<td>A</td>
<td>2 × 500 mg</td>
<td>7–10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C</td>
<td>1 × 500 mg</td>
<td>1 × 500 mg</td>
</tr>
<tr>
<td>Multiple EM LNB</td>
<td>As for EM above</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ceftriaxone</td>
<td>i.v.</td>
<td>A</td>
<td>2 g/kg</td>
<td>14 (10–28)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C</td>
<td>20 Mio</td>
<td>Same</td>
</tr>
<tr>
<td></td>
<td>Penicillin G</td>
<td>i.v.</td>
<td>A</td>
<td>18–24 Mio in 4 divided doses</td>
<td>14 (10–28)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C</td>
<td>0.2–0.4 Mio/kg</td>
<td></td>
</tr>
<tr>
<td>Arthritis</td>
<td>Cefotaxime</td>
<td>i.v.</td>
<td>A</td>
<td>2 g every 8 h</td>
<td>(10–28)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C</td>
<td>150–200 mg/kg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Doxycycline may be adequate)(a)</td>
<td>oral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Doxycycline</td>
<td>Oral</td>
<td>A</td>
<td>2 × 100 mg</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C</td>
<td>3 × 500 mg</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Amoxicillin</td>
<td>Oral</td>
<td>A</td>
<td>2 × 500 mg</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Cefuroxime axetil</td>
<td>Oral</td>
<td>A</td>
<td>30 mg/kg in 2 divided doses</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C</td>
<td>2 × 500 mg</td>
<td>28</td>
</tr>
<tr>
<td>ACG</td>
<td>Ceftriaxone</td>
<td>i.v.</td>
<td>A</td>
<td>2 g/kg</td>
<td>21 (14–30)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C</td>
<td>2 g/kg</td>
<td>21 (14–30)</td>
</tr>
<tr>
<td>Cardio-</td>
<td>Ceftriaxone</td>
<td>Oral</td>
<td>A</td>
<td>2 g</td>
<td>21 (14–30)</td>
</tr>
<tr>
<td>borbolosis</td>
<td></td>
<td></td>
<td>C</td>
<td>2 g/kg</td>
<td>21 (14–30)</td>
</tr>
<tr>
<td></td>
<td>Doxycycline</td>
<td>Oral</td>
<td>A</td>
<td>2 × 100 mg</td>
<td>21 (14–30)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C</td>
<td>3 × 500 mg</td>
<td>21 (14–30)</td>
</tr>
</tbody>
</table>

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\(a\) In Europe, azithromycin is primarily considered as an alternative treatment for patients who should not take doxycycline and are allergic to penicillin, such as children and pregnant or breastfeeding women.

\(b\) Doxycycline is not recommended for children <8 years of age or pregnant or breastfeeding women.

\(c\) Macrolide antibiotics are less effective than other antimicrobials and should be reserved for patients for whom amoxicillin, doxycycline and cefuroxime axetil are contraindicated.

\(d\) In a non-inferiority RCT, oral doxycycline was shown as effective as i.v. ceftriaxone for the treatment of European LNB [228], confirming the results of earlier open-label studies [221], but it is not yet clear whether this extends to North American patients with neurological manifestations.
**Controversy # 1 - Treatment Recommendations IDSA**

Table 4. Selected antimicrobials, drug regimens, or other modalities *not* recommended for the treatment of Lyme disease.

<table>
<thead>
<tr>
<th>Doses of antimicrobials far in excess of those provided in tables 2 and 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple, repeated courses of antimicrobials for the same episode of Lyme disease or a duration of antimicrobial therapy prolonged far in excess of that shown in table 3</td>
</tr>
<tr>
<td>Combination antimicrobial therapy</td>
</tr>
<tr>
<td>Pulsed-dosing (i.e., antibiotic therapy on some days but not on other days)</td>
</tr>
<tr>
<td>First-generation cephalosporins, benzathine penicillin G, fluoroquinolones, carbapenems, vancomycin, metronidazole, tinidazole, trimethoprim-sulfamethoxazole, amantadine, ketolides, isoniazid, or fluconazole</td>
</tr>
<tr>
<td>Empirical antibabesiosis therapy in the absence of documentation of active babesiosis</td>
</tr>
<tr>
<td>Anti-<em>Bartonella</em> therapies</td>
</tr>
<tr>
<td>Hyperbaric oxygen therapy</td>
</tr>
<tr>
<td>Fever therapy (with or without malaria induction)</td>
</tr>
<tr>
<td>Intravenous immunoglobulin</td>
</tr>
<tr>
<td>Ozone</td>
</tr>
<tr>
<td>Cholestyramine</td>
</tr>
<tr>
<td>Intravenous hydrogen peroxide</td>
</tr>
<tr>
<td>Vitamins or nutritional managements</td>
</tr>
<tr>
<td>Magnesium or bismuth injections</td>
</tr>
</tbody>
</table>

Different Recommendations

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EXECUTIVE SUMMARY

Background

Lyme disease is the most common tick-borne infection in both North America and Europe. In the United States, Lyme disease is caused by Borrelia burgdorferi, which is transmitted by the bite of the tick species Ixodes dammini and bovis. Clinical manifestations most often involve the skin, joints, nervous system, and heart. Neurological manifestations are less commonly seen than in earlier years. Early cutaneous infections with B. burgdorferi are called erythema migrans, which is the most common clinical manifestation of Lyme disease. I. scapularis may also be infected with and transmit Anaplasma phagocytophilum (previously referred to as Anaplasma phagocytophilum and formerly Rickettsia) Originalia lama, the primary cause of human granulocytic anaplasmosis, a new tick-borne disease that may lead to the development of disease in humans. Human granulocytic anaplasmosis (HGA, formerly known as human granulocytic ehrlichiosis), or ehrlichiosis, as a single infection, less frequently, as a co-infection. Clinical findings are suggestive

Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease

Daniel J. Cameron, Lorraine B Johnson & Elizabeth L. Maloney

To cite the article: Daniel J. Cameron, Lorraine B Johnson & Elizabeth L. Maloney (2014) Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease. Expert Review of Anti-infective Therapy, 11:9, 1139-1139, DOI: 10.1586/14783649.11.9.1139

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Diagnosis of Lyme Disease

- Erythema migrans is the only reliable physical finding that can be used to diagnose Lyme disease.

- No confirmatory serologic testing recommended for patients with early Lyme disease.

- Approximately **20 - 40 %** of patients with early localized Lyme disease are seropositive.

Diagnosis of Lyme Disease


<table>
<thead>
<tr>
<th>SUN</th>
<th>MON</th>
<th>TUE</th>
<th>WED</th>
<th>THU</th>
<th>FRI</th>
<th>SAT</th>
</tr>
</thead>
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<td>28</td>
<td>29</td>
<td>30</td>
</tr>
</tbody>
</table>

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Diagnosis of Lyme Disease

Low sensitivity of serologic test during early disease

IgG+ Low sensitivity of serologic test during early disease

IgM+
Diagnosis of Lyme Disease

• Serologic testing should be performed only if:

  — A recent history of having resided in or traveled to an area endemic for Lyme disease

  — A risk factor for exposure to ticks

  — Symptoms consistent with early disseminated disease or late Lyme disease

Lyme disease Testing Algorithm

Two-Tiered Testing for Lyme Disease

First Test
- Enzyme Immunoassay (EIA)
  - OR
  - Immunofluorescence Assay (IFA)

Second Test
- Signs or symptoms ≤ 30 days
  - IgM and IgG Western Blot
- Signs or symptoms > 30 days
  - IgG Western Blot ONLY

Consider alternative diagnosis
OR
If patient with signs/symptoms consistent with Lyme disease for ≤ 30 days, consider obtaining a convalescent serum

National Center for Emerging and Zoonotic Infectious Diseases
Division of Vector Borne Diseases | Bacterial Diseases Branch
Sensitivity and Specificity ELISA

Table 3. Sensitivity, Specificity, and Likelihood Ratios of Enzyme-Linked Immunosorbent Assay*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Likelihood Ratio</th>
<th>Negative Likelihood Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Lyme disease†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study by Dressler et al. (44) (57 patients with Lyme disease; 139 controls)</td>
<td>40</td>
<td>94</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDC study (45) (58 patients with Lyme disease; 113 controls)</td>
<td>78</td>
<td>89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Random-effects combined estimate</td>
<td>59</td>
<td>93</td>
<td>8.42</td>
<td>0.44</td>
</tr>
<tr>
<td>Late Lyme disease‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study by Dressler et al. (44) (98 patients with Lyme disease; 139 controls)</td>
<td>89</td>
<td>72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDC study (45) (49 patients with Lyme disease; 113 controls)</td>
<td>100</td>
<td>89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Random-effects combined estimate</td>
<td>95</td>
<td>81</td>
<td>5.01</td>
<td>0.06</td>
</tr>
</tbody>
</table>

* Indeterminate results were considered positive for these analyses. CDC = Centers for Disease Control and Prevention.
† Serum samples were obtained from patients with erythema migrans.
‡ Testing was done after the first weeks of infection.
Treatment of Early Disease and Seroconversion

- Antibiotic treatment in early Lyme disease may prevent seroconversion

Vaccination and Seroconversion

- **LYMEX** induces antibodies that can cause a positive ELISA and WB
New Diagnostic approach - Single step VlsE C6 ELISA

- IgG antibodies develop within the first week with comparable sensitivity and specificity to IgM ELISA tests

Table 3. Sensitivity and specificity of 2-tier testing, compared with that of an ELISA that employs a 26-mer peptide from the sixth invariant region (C6) of the variable major protein-like sequence-expressed (VlsE) lipoprotein of the spirochete Borrelia burgdorferi in a cohort of patients with various manifestations of Lyme disease.

<table>
<thead>
<tr>
<th>Variable</th>
<th>IgM</th>
<th></th>
<th></th>
<th>IgM or IgG</th>
<th></th>
<th></th>
<th>IgG VlsE C6 peptide ELISA</th>
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<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>Sensitivity</td>
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<tr>
<td>Erythema migrans</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute phase</td>
<td>25</td>
<td>99</td>
<td>11</td>
<td>99</td>
<td>29</td>
<td>99</td>
<td>29</td>
</tr>
<tr>
<td>Convalescent phase</td>
<td>55</td>
<td>99</td>
<td>18</td>
<td>99</td>
<td>64</td>
<td>99</td>
<td>56</td>
</tr>
<tr>
<td>Acute neurologic or cardiac abnormalities</td>
<td>85</td>
<td>99</td>
<td>85</td>
<td>99</td>
<td>100</td>
<td>99</td>
<td>100</td>
</tr>
<tr>
<td>Arthritis or chronic neurologic abnormalities</td>
<td>NA</td>
<td>...</td>
<td>100</td>
<td>99</td>
<td>100</td>
<td>99</td>
<td>100</td>
</tr>
</tbody>
</table>

NOTE. Sensitivity was determined on the basis of serum samples from 76 patients with erythema migrans, 13 patients with acute neurologic or cardiac abnormalities, and 31 patients with arthritis or chronic neurologic abnormalities. Specificity was determined on the basis of serum samples from 86 healthy subjects from an area in which Lyme disease was endemic and serum samples from 50 subjects from an area in which Lyme disease was not endemic. NA, not applicable.
New Diagnostic approach – Replacement of WB for VlsE C6 ELISA

The specificity of ELISA followed by VlsE C6 ELISA was equivalent to that of ELISA followed by Western blot and more specific than VlsE C6 ELISA alone.

Table 4. Overall Performance of the Proposed 2-EIA Algorithm

<table>
<thead>
<tr>
<th>Patients with active Lyme disease</th>
<th>Standard 2-tiered algorithm</th>
<th>2-EIA algorithm</th>
<th>C6 EIA alone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. +</td>
<td>Sens (%)</td>
<td>Spec (%)</td>
</tr>
<tr>
<td>Early Disease (N = 140)</td>
<td>67</td>
<td>48</td>
<td>–</td>
</tr>
<tr>
<td>Stage 1: Erythema migrans (N = 114)</td>
<td>48</td>
<td>42</td>
<td>–</td>
</tr>
<tr>
<td>Stage 2: Acute neuritis or carditis (N = 26)</td>
<td>19</td>
<td>73</td>
<td>–</td>
</tr>
<tr>
<td>Late Disease (N = 29)</td>
<td>29</td>
<td>100</td>
<td>–</td>
</tr>
<tr>
<td>Stage 3: Arthritis or late neuritis (N = 29)</td>
<td>96</td>
<td>57</td>
<td>–</td>
</tr>
<tr>
<td>All Patients (N = 169)</td>
<td>7</td>
<td>–</td>
<td>99.5</td>
</tr>
<tr>
<td>Control Subjects (N = 1300)</td>
<td>7</td>
<td>–</td>
<td>99.5</td>
</tr>
</tbody>
</table>

NOTE. EIA, enzyme immunoassay; No., number; Sens, sensitivity; Spec, specificity.  
* The P values pertain to the comparison with the standard 2-tiered algorithm.
CSF Serology

- CSF serology is not recommended for diagnosis of neurologic involvement of Lyme disease

- Intratechial Ab measurement can be useful in certain circumstances (not useful in peripheral disease)

- Sensitivity of CSF serology is unclear (most studies are from Europe), although some studies report 90% sensitivity

**B. Burgdorferi** PCR

- CSF or synovial fluid PCR can add confirmatory information in seropositive patients

- CSF PCR has low sensitivity with significant false positives

- *Borrelia* DNA can be detected in synovial fluid in up to 85% of patients with Lyme arthritis

### TABLE 3. Sensitivities and specificities of PCR assays for detection of *B. burgdorferi* DNA in different clinical specimens from patients with LB

<table>
<thead>
<tr>
<th>Clinical specimen and region</th>
<th>No. of studies included</th>
<th>Median % sensitivity (range)</th>
<th>Reported % specificity range</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin biopsy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EM</td>
<td>16</td>
<td>69 (36-88)</td>
<td>98-100</td>
<td>177, 301, 303, 327</td>
</tr>
<tr>
<td>United States</td>
<td>4</td>
<td>64 (59-67)</td>
<td>98-100</td>
<td>31, 165, 209-211, 234, 256, 272, 279, 344, 358, 359</td>
</tr>
<tr>
<td>Europe</td>
<td>12</td>
<td>73 (36-88)</td>
<td>100</td>
<td>31, 199, 209, 210, 256, 279, 344, 359</td>
</tr>
<tr>
<td>ACA, Europe</td>
<td>8</td>
<td>76 (54-100)</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Blood, plasma, serum</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>6</td>
<td>14 (0-100)</td>
<td>100</td>
<td>108, 172, 345</td>
</tr>
<tr>
<td>Europe</td>
<td>3</td>
<td>18 (0-59)</td>
<td>100</td>
<td>78, 233, 234</td>
</tr>
<tr>
<td>CSF</td>
<td>16</td>
<td>38 (12-100)</td>
<td>93-100</td>
<td>134, 150, 172, 180, 223, 239</td>
</tr>
<tr>
<td>United States</td>
<td>6</td>
<td>73 (25-93)</td>
<td>93-100</td>
<td>11, 57, 74, 88, 130, 162, 233, 236, 270, 377</td>
</tr>
<tr>
<td>Europe</td>
<td>10</td>
<td>23 (12-100)</td>
<td>98-100</td>
<td></td>
</tr>
<tr>
<td>Synovial fluid</td>
<td>8</td>
<td>78 (42-100)</td>
<td>100</td>
<td>30, 172, 224, 252</td>
</tr>
<tr>
<td>United States</td>
<td>4</td>
<td>83 (76-100)</td>
<td>100</td>
<td>87, 133, 270, 293</td>
</tr>
<tr>
<td>Europe</td>
<td>4</td>
<td>66 (42-85)</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

*Only studies published in MEDLINE-indexed periodicals during the years 1991 to 2003 and those examined by PCR assay for ≥5 cases are included.

* Median sensitivity of PCR assays based on included studies. For studies tested with multiple PCR primer sets, the highest sensitivity reported was selected for analysis.

* NA, not available.
PCR Limitations

- PCR does not distinguish between living and dead organisms

- Laboratory contamination with amplified DNA poses a risk for false-positive results

- No PCR-based assays is currently cleared by the FDA
**B. Burgdorferi Culture**

### TABLE 2. Cultivation of Lyme borreliae from clinical samples

<table>
<thead>
<tr>
<th>Site</th>
<th>Representative culture yield (%) (reference[s])</th>
<th>United States</th>
<th>Europe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythema migrans</td>
<td>&gt;50&lt;sup&gt;a&lt;/sup&gt; (25, 200, 204, 214, 227, 303, 327, 369)</td>
<td></td>
<td>≥40&lt;sup&gt;b&lt;/sup&gt; (14, 31, 140, 165, 209, 237, 256, 333, 342, 380)</td>
</tr>
<tr>
<td>Acrodermatitis chronica atrophicans</td>
<td>ND&lt;sup&gt;h&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Borrelial lymphocytoma</td>
<td>ND</td>
<td></td>
<td>≥22&lt;sup&gt;c&lt;/sup&gt; (14, 258, 342)</td>
</tr>
<tr>
<td>Cerebrospinal fluid</td>
<td>ND</td>
<td></td>
<td>24 (188)</td>
</tr>
<tr>
<td>Synovial fluid</td>
<td>Anecdotal</td>
<td></td>
<td>10&lt;sup&gt;d&lt;/sup&gt; (60, 147, 237, 342)</td>
</tr>
<tr>
<td>Blood</td>
<td>&gt;40&lt;sup&gt;e&lt;/sup&gt; (367, 368)</td>
<td></td>
<td>Anecdotal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.2&lt;sup&gt;f&lt;/sup&gt; to 9&lt;sup&gt;g&lt;/sup&gt; (13, 189)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Highest reported yield, 86% (25).
<sup>b</sup> Highest reported yield, 88% (342).
<sup>c</sup> Highest reported yield, 60% (342).
<sup>d</sup> Highest reported yield, 17% (342).
<sup>e</sup> Plasma (high volume, ≥9 ml) of untreated adult United States patients with erythema migrans.
<sup>f</sup> Plasma (low volume, ≤3 ml) of European adults with erythema migrans.
<sup>g</sup> Plasma (low volume, <1 ml) of untreated European children with erythema migrans.
<sup>h</sup> ND, no data available.
Controversy # 2
Test Not Recommended by CDC-IDSA

• Capture assays for antigens in urine

• Culture, immunofluorescence staining, or cell sorting of cell wall-deficient or cystic forms

• 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 tests without a previous ELISA/EIA/IFA

http://www.cdc.gov/lyme/diagnostictesting/labtest/otherlab/index.html
Reinfection with *B. burgdorferi*

- A previous infection does not protect from reinfection
  - Erythema migrans is the most common sign of reinfection
  - Strain-specific immunity lasts for approximately 6 years
  - No reinfection has been reported in patients who suffered late disease (Lyme arthritis)

Controversy #3 - Post Lyme Syndrome vs. Chronic Lyme

No consensus of the definition
Controversy # 3 - Post Lyme Syndrome vs. Chronic Lyme

The patients who have had well-documented Lyme disease and who remain symptomatic for many months to years after completion of appropriate antibiotic therapy.
The Four Predominant Categories of Disease Associated with Chronic Lyme Disease

<table>
<thead>
<tr>
<th>Category 1</th>
<th>Category 2</th>
<th>Category 3</th>
<th>Category 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms of unknown cause, with no evidence of <em>Borrelia burgdorferi</em> infection</td>
<td>A well-defined illness unrelated to <em>B. burgdorferi</em> infection</td>
<td>Symptoms of unknown cause, with antibodies against <em>B. burgdorferi</em> but no history of objective clinical findings that are consistent with Lyme disease</td>
<td>Post–Lyme disease syndrome</td>
</tr>
</tbody>
</table>

Controversy # 3 – Post Lyme Syndrome vs. Chronic Lyme

Table 5. Proposed definition of post-Lyme disease syndrome.

Inclusion criteria
- An adult or child with a documented episode of early or late Lyme disease fulfilling the case definition of the Centers for Disease Control and Prevention [112]. If based on erythema migrans, the diagnosis must be made and documented by an experienced health care practitioner.
- After treatment of the episode of Lyme disease with a generally accepted treatment regimen [146] (Tables 2 and 3), there is resolution or stabilization of the objective manifestations of Lyme disease.
- Onset of any of the following subjective symptoms within 6 months of the diagnosis of Lyme disease and persistence of continuous or relapsing symptoms for at least a 6 month period after completion of antibiotic therapy:
  - Fatigue
  - Widespread musculoskeletal pain
  - Complaints of cognitive difficulties
- Subjective symptoms are of such severity that, when present, they result in substantial reduction in previous levels of occupational, educational, social, or personal activities.

Exclusion criteria
- An active, untreated, well-documented coinfection, such as babesiosis.
- The presence of objective abnormalities on physical examination or on neuropsychologic testing that may explain the patient’s complaints. For example, a patient with antibiotic refractory Lyme arthritis would be excluded. A patient with late neuroborreliosis associated with encephalopathy, who has recurrent or refractory objective cognitive dysfunction, would be excluded.
- A diagnosis of fibromyalgia or chronic fatigue syndrome before the onset of Lyme disease.
- A prolonged history of undiagnosed or unexplained somatic complaints, such as musculoskeletal pains or fatigue, before the onset of Lyme disease.
- A diagnosis of an underlying disease or condition that might explain the patient’s symptoms (e.g., morbid obesity, with a body mass index [calculated as weight in kilograms divided by the square of height in meters] >45; sleep apnea and narcolepsy; side effects of medications; autoimmune diseases; uncontrolled cardiopulmonary or endocrine disorders; malignant conditions within 2 years, except for uncomplicated skin cancer; known current liver disease; any past or current diagnosis of a major depressive disorder with psychotic or melancholic features; bipolar affective disorders; schizophrenia of any subtype; delusional disorders of any subtype; dementia of any subtype; anorexia nervosa or bulimia nervosa; and active drug abuse or alcoholism at present or within 2 years).
- Laboratory or imaging abnormalities that might suggest an undiagnosed process distinct from post-Lyme disease syndrome, such as a highly elevated erythrocyte sedimentation rate (>50 mm/h); abnormal thyroid function; a hematologic abnormality; abnormal levels of serum albumin, total protein, globulin, calcium, phosphorus, glucose, urea nitrogen, electrolytes, or creatinine; significant abnormalities on urine analysis; elevated liver enzyme levels; or a test result suggestive of the presence of a collagen vascular disease.
- Although testing by either culture or PCR for evidence of Borrelia burgdorferi infection is not required, should such testing be done by reliable methods, a positive result would be an exclusion.

Post Lyme Syndrome vs. Chronic Lyme

- The term chronic Lyme disease is frequently used to describe patients with vague complaints who have never had Lyme disease
  - Fatigue
  - Cognitive decline
  - Generalized muscle and joint aches
Post Lyme Syndrome vs. Chronic Lyme

• No evidence of long lasting infection in patients who received appropriate treatment
Post Lyme Syndrome vs. Chronic Lyme

- **New novel culture** for *B. burgdorferi*
  - 47 patients who had been extensively treated with antimicrobials for symptoms of “chronic Lyme disease”.
  - Study reported a 97% blood culture positivity rate
  - Culture medium **required Detroit tap water** as a constituent
  - PCR data necessary to confirm spirochetes were *B. burgdorferi* was missing
  - Another study was not able to replicate findings on the novel or traditional *B. burgdorferi* culture medium


Post Lyme Syndrome vs. Chronic Lyme

- Positive PCR in urine samples of 74.2% of 97 US patients who were diagnosed as having chronic Lyme disease and who were treated with extended course of antibiotics.

- Authors did not sequence the amplicons to confirm identity.
Post Lyme Syndrome vs. Chronic Lyme

- Prolonged antibiotic therapy (more than 28 days) is not indicated for treatment of any stage of Lyme disease

Figure 1. Change or Lack of Change from Baseline in the Health-Related Quality of Life as Measured by the Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36).

Results are shown for the overall outcome (Panel A, all patients; Panel D, seropositive patients; Panel G, seronegative patients); the physical component (Panel B, all patients; Panel E, seropositive patients; Panel H, seronegative patients); and the mental component (Panel C, all patients; Panel F, seropositive patients; Panel I, seronegative patients). The scores of patients in the antibiotic group are compared with those of patients in the placebo group at the end of intravenous treatment (day 30), at the end of oral treatment (day 90), and 3 months after the completion of treatment (day 180). Statistical tests comparing the scores in the antibiotic group with those in the placebo group showed no statistically significant difference at any of the time points.

Post Lyme Syndrome vs. Chronic Lyme

• Prolonged antibiotic therapy (more than 28 days) is not indicated for treatment of any stage of Lyme disease

  “A 30-year-old woman died as a result of a large Candida parapsilosis septic thrombus located on the tip of a Groshong catheter. The catheter had been in place for 28 months for administration of a 27 month course of intravenous cefotaxime for an unsubstantiated diagnosis of chronic Lyme disease.”
Post Lyme Syndrome vs. Chronic Lyme

- Prolonged antibiotic therapy (more than 28 days) is not indicated for treatment of any stage of Lyme disease.
Post Lyme Syndrome vs. Chronic Lyme

• **Evaluation for other causes of symptoms**
  
  — Coinfections with other tick-borne illnesses
    
    • *Ehrlichia and Anaplasma*
    
    • *Babesia*
  
  — Fibromyalgia
  
  — Depression
  
  — Hypothyroidism
  
  — Malignancies
Conclusion

• There is effective treatment for all stages of Lyme disease

• Two tier diagnostic algorithm is an useful protocol for diagnosis of Lyme, although sensitivity is poor during early stage of disease

• PCR has limited utility in the diagnosis of Lyme disease and most be used only in certain circumstances

• No evidence of benefit of prolonged antibiotic therapy for patients suffering from post Lyme syndrome
Thank You !!!

Questions ???