Lyme Disease

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Lyme Disease: An Infectious Disease

• Beginning
  – Tick bites person

• Middle
  – Person gets sick
  – Diagnosis is made

• End
  – Antibiotic kills bacteria
  – Person gets better
Lyme Disease: A Brief History

- Late 1970s – Investigation of “outbreak” of juvenile rheumatoid arthritis in Old Lyme, Connecticut
- 1980s
  - More cases in northeastern U.S. and Mid-Atlantic region
  - *Borrelia burgdorferi* identified as cause
  - Antibiotics shown to treat and cure most cases
- 1990s – wider geographic spread
Lyme Disease: A Brief History

- Late 1980s and 1990s – several tests developed to identify infection
  - Immunofluorescent antibody (IFA)
  - ELISA (a.k.a. EIA – enzyme immunoassay)
  - Western blot
  - T-lymphocyte stimulation test

- These tests sometimes unreliable
  - Inter- and intra-laboratory variability
Lyme Disease: A Brief History

- **1990s**
  - Many physicians unaware
  - Variable test reliability
  - Many patients went undiagnosed (or diagnosed late)
    - Often with bad outcomes
  - Some physicians became self-styled Lyme experts and spread alternative information
Lyme Disease: A Brief History

- 1990s and 2000s
  - Internet
    - Variably reliable information
  - Diagnostic testing improves
  - More physicians aware / testing for infection
  - Antibiotic treatment approaches refined
    - Best antibiotic agents
    - Appropriate duration
  - Lyme vaccine briefly available
Lyme Disease: A Brief History

- Lyme “community”
  - Lyme-literate physicians
  - Clinical diagnosis
  - Standard tests unreliable
  - Alternative tests / labs
  - Chronic Lyme Disease
  - Longer treatment courses, based on symptoms
  - Treatment other than beta-lactams / doxycycline

- “Mainstream” medicine
  - Most providers competent to manage EM and uncomplicated cases
    - Not always
  - Specialists
    - Neurologists
    - Rheumatologists
    - Infectious diseases
  - Reliance on standard tests
  - Evidence-based therapy
Borrelia burgdorferi
“I hope that we never lose sight of one fact: that this was all started by a mouse.”  W. Disney
Ixodes scapularis
Adult female, adult male, nymph, larva
Larva feeds on small animals, particularly the white-footed mouse, and becomes infected with bacteria that cause Lyme disease.

Female tick drops off deer host and lays eggs on the ground.

Nymph grows to adult tick, which feeds on large animals, particularly deer. At this stage, the tick also mates.

Infected nymph bites and transmits Lyme disease to host—another animal or person.

Larva molts into a nymph—the most aggressive stage.

Larva is dormant.
Lyme Disease: Epidemiology

- Endemic in areas with *Ixodes* ticks and vector-competent host animals
- Early disease most common from late spring to early fall
- Late disease may be seen year round
- Outdoor activity (occupational, leisure) increases risk
Reported Cases of Lyme Disease, United States. CDC estimates true annual incidence is 300,000. With an incidence of 41 per 100,000 population, Delaware ranks 6th in nation.
Confirmed Case of Lyme Disease by Age and Sex, United States
Lyme Disease: More Epidemiology

- Early LD most common in April - Sept.
- Late LD (arthritis) may occur year round
- Location of residence, occupational and leisure activity may be risk factors
<table>
<thead>
<tr>
<th>Disease stage</th>
<th>Timing after tick bite</th>
<th>Clinical manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early localized</td>
<td>3 – 30 days</td>
<td>EM (single) Myalgia, arthralgia, fever, headache, fatigue</td>
</tr>
<tr>
<td>Early disseminated</td>
<td>3 – 12 weeks</td>
<td>EM (single or multiple) Constitutional sx Meningitis Radiculoneuritis Cranial Neuritis Carditis Ocular disease</td>
</tr>
<tr>
<td>Late disease</td>
<td>&gt; 2 months</td>
<td>Arthritis Chronic neurologic dis.</td>
</tr>
</tbody>
</table>
Early Localized Disease
Generally painless

Slowly expand, sometimes > 20 cm
Early Disseminated Disease
Early Disease – Other Manifestations
May Present w/ or w/o EM

- Fatigue 54%
- Anorexia 26
- Headache 42
- Neck stiffness 35
- Myalgias 44
- Arthralgias 44
- Regional lymphadenopathy 23
- Fever 16
Cranial Neuropathy

- II vision loss
- III, IV, VI diplopia
- V facial pain, paraesthesia
- VII facial weakness
- VIII hearing loss, dizziness
- IX, X dysphagia, hoarseness
- XI neck weakness
- XII tongue weakness
Lyme Disease-Associated Peripheral Facial Nerve Palsy

- 3-14% of Lyme disease presents with PFNP
- 25-50% of facial palsies in Lyme endemic areas
- Frequently associated with CNS disease (especially pleocytosis), often without overt meningeal signs / symptoms
- Mechanism of facial nerve damage and relationship to CNS disease not completely clear
Lyme Meningitis: Clinical

- Over 90% of children with Lyme meningitis will have one or more
  - Erythema migrans
  - Cranial neuropathy
  - Papilledema
- Compared with viral meningitis
  - Longer duration
  - Less fever
Lyme Meningitis: CSF

- **Non-specific**
  - pleocytosis, usually lymphs/monos (91% vs. 56% in viral meningitis)
  - normal to mildly depressed glucose
  - normal to mildly elevated protein

- **Specific**
  - *B. burgdorferi* specific antibody
  - PCR – poor sensitivity
Rhythm strip from child with Lyme disease
Late Disease

- Arthritis
  - oligoarticular, large joints
  - swelling, warmth, decreased ROM
  - knee > ankle > upper extremity
  - recurrent attacks
  - high WBC in synovial fluid
Lyme Arthritis

- Small subset of patients have treatment resistant arthritis
- Evidence suggests post-infectious immunoreactivity more likely than ongoing infection
- Possible role for synovectomy
- Treatment as for chronic inflammatory arthropathies
Chronic CNS Lyme Disease

- Lyme Disease Foundation (partial list)
  - dizziness
  - fainting
  - drooping shoulders
  - confusion
  - word finding difficulty
  - panic attacks
  - impulsive violence

- Must be objectively defined by neurologic findings, CSF findings, or imaging
- Lyme encephalopathy - active infection
- Persistent ICP

See excellent reference
Coinfections

- *Ixodes scapularis* also transmits
  - *Anaplasma phagocytophilum* (anaplasmosis)
  - *Babesia microti* (babesiosis)
- Associated with more severe and prolonged symptoms, especially fever
- Seen in restricted geographic regions
Lyme Disease: Diagnosis

- Erythema migrans is diagnostic
- Enzyme immunoassay (EIA / ELISA) usually positive by 3\textsuperscript{rd} week
- Western blot (IgM and IgG) recommended for confirming a positive or equivocal EIA
- C6 antibody test has greater specificity
- \textit{All you will ever need to order is the EIA and reflex western blot}
Weeks

Early Localized

IgM

Early Disseminated

IgG

Late Disease

Months
Positive Antibody Tests

- Background seropositivity in some communities is as high as 8%
  - caution must be used in interpreting serologic test results for non-classical symptoms
- Many patients remain IgG positive for years
- IgM may remain or reappear in some cases
- Many causes for false positive ELISA
  - viral infections, e.g. EBV
  - autoimmune diseases
  - other spirochetal infections
Negative Antibody Tests

- Early disease may be seronegative
- Antibiotic therapy may blunt antibody response

**HOWEVER**
- True seronegative Lyme disease (i.e. active infection) in later stages is uncommon
Western blot for *B. burgdorferi* antibodies

- IgM Western Blot
  - 23 kD
  - 39
  - 41
- Requires 2 of 3

- IgG Western Blot
  - 18 kD
  - 23
  - 28
  - 30
  - 39
  - 41
  - 45
  - 58
  - 66
  - 93
- Requires 5 of 10
Two Test Approach

- ELISA: Quantitative, sensitive
- Western blot: Qualitative, specific
Two-Tiered Testing for Lyme Disease

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

  **Flowchart Diagram**:
  - Positive or Equivocal Result
    - Signs or symptoms ≤ 30 days: IgM and IgG Western Blot
    - Signs or symptoms > 30 days: IgG Western Blot ONLY
  - Negative Result
    - Consider alternative diagnosis
      - OR
      - If patient with signs/symptoms consistent with Lyme disease for ≤ 30 days, consider obtaining a convalescent serum

**Second Test**
- IgM and IgG Western Blot
- IgG Western Blot ONLY

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*National Center for Emerging and Zoonotic Infectious Diseases*
*Division of Vector Borne Diseases | Bacterial Diseases Branch*
Follow-up serologic testing is hardly ever required.
PCR for *B. burgdorferi*

- **Skin:** Works, but don’t need it
- **Arthritis:** Works and often helpful
- **CNS:** Doesn’t work well, but we sometimes need it
Some laboratories offer Lyme disease testing using assays whose accuracy and clinical usefulness have not been adequately established. Unvalidated tests available as of 2011 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 tests without a previous ELISA/EIA/IFA
In general, testing of individual ticks is not useful because:

- If the test shows that the tick contained disease-causing organisms, that does not necessarily mean that you have been infected.
- If you have been infected, you will probably develop symptoms before results of the tick test are available. You should not wait for tick testing results before beginning appropriate treatment.
- Negative results can lead to false assurance. For example, you may have been unknowingly bitten by a different tick that was infected.
Treatment Guidelines

- Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease, by the International Lyme and Associated Diseases Society
- Beware of what patients may read on the Internet!!!
Remedies for Lyme Disease

- Lyme disease diet
- Borage seed oil
- CoQ10
- Carnitine
- Herbal extracts
- Fish oil
- Chelation therapy

- Body cleansing
- Accupuncture
- Homeopathic remedies
- Chiropractic
- Thymic protein A
- Transfer factor
- Antibiotics
Table 2. Recommended antimicrobial regimens for treatment of patients with Lyme disease.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage for adults</th>
<th>Dosage for children</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preferred oral regimens</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>500 mg 3 times per day&lt;sup&gt;a&lt;/sup&gt;</td>
<td>50 mg/kg per day in 3 divided doses (maximum, 500 mg per dose)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>100 mg twice per day&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Not recommended for children aged &lt;8 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>For children aged ≥8 years, 4 mg/kg per day in 2 divided doses (maximum, 100 mg per dose)</td>
</tr>
<tr>
<td>Cefuroxime axetil</td>
<td>500 mg twice per day</td>
<td>30 mg/kg per day in 2 divided doses (maximum, 500 mg per dose)</td>
</tr>
<tr>
<td><strong>Alternative oral regimens</strong></td>
<td>For recommended dosing regimens, see footnote&lt;sup&gt;d&lt;/sup&gt; in table 3</td>
<td>For recommended dosing regimens, see footnote in table 3</td>
</tr>
<tr>
<td>Selected macrolides&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>For recommended dosing regimens, see footnote&lt;sup&gt;d&lt;/sup&gt; in table 3</td>
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</tr>
<tr>
<td><strong>Preferred parenteral regimen</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>2 g intravenously once per day</td>
<td>50–75 mg/kg intravenously per day in a single dose (maximum, 2 g)</td>
</tr>
<tr>
<td><strong>Alternative parenteral regimens</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>2 g intravenously every 8 h&lt;sup&gt;d&lt;/sup&gt;</td>
<td>150–200 mg/kg per day intravenously in 3–4 divided doses (maximum, 6 g per day)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Penicillin G</td>
<td>18–24 million U per day intravenously, divided every 4 h&lt;sup&gt;d&lt;/sup&gt;</td>
<td>200,000–400,000 U/kg per day divided every 4 h&lt;sup&gt;d&lt;/sup&gt; (not to exceed 18–24 million U per day)</td>
</tr>
</tbody>
</table>

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<sup>a</sup> Although a higher dosage given twice per day might be equally as effective, in view of the absence of data on efficacy, twice-daily administration is not recommended.

<sup>b</sup> Tetracyclines are relatively contraindicated in pregnant or lactating women and in children <8 years of age.

<sup>c</sup> Because of their lower efficacy, macrolides are reserved for patients who are unable to take or who are intolerant of tetracyclines, penicillins, and cephalosporins.

<sup>d</sup> Dosage should be reduced for patients with impaired renal function.
Antibiotics for Lyme Disease

- Amoxicillin
- Doxycycline
- Cefuroxime axetil
- Ceftriaxone (IV)
Doxycycline

- Excellent oral bioavailability
- Lipophilic
- Good CNS penetration (26%)
- Active vs. *Anaplasma* as well as *B. burgdorferi*
- 2 week course does not stain teeth
- Precautions:
  - photosensitivity reactions
  - esophageal burns
<table>
<thead>
<tr>
<th>Indication</th>
<th>Treatment</th>
<th>Duration, days (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tick bite in the United States</td>
<td>Doxycycline, 200 mg in a single dose(^{a,b}); (4 mg/kg in children ≥8 years of age) and/or observation</td>
<td>...</td>
</tr>
<tr>
<td>Erythema migrans</td>
<td>Oral regimen(^{c,d})</td>
<td>14 (14–21)(^{b})</td>
</tr>
<tr>
<td>Early neurologic disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningitis or radiculopathy</td>
<td>Parenteral regimen(^{a,f})</td>
<td>14 (10–28)</td>
</tr>
<tr>
<td>Cranial nerve palsy(^{a,g})</td>
<td>Oral regimen(^{c})</td>
<td>14 (14–21)</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>Oral regimen(^{a,c,h}) or parenteral regimen(^{a,c,h})</td>
<td>14 (14–21)</td>
</tr>
<tr>
<td>Borreliotic lymphocytoma</td>
<td>Oral regimen(^{c,d})</td>
<td>14 (14–21)</td>
</tr>
<tr>
<td>Late disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthritis without neurologic disease</td>
<td>Oral regimen(^{c})</td>
<td>28</td>
</tr>
<tr>
<td>Recurrent arthritis after oral regimen</td>
<td>Oral regimen(^{a,c}) or parenteral regimen(^{a,c})</td>
<td>14 (14–28)</td>
</tr>
<tr>
<td>Antibiotic-refractory arthritis(^{i})</td>
<td>Symptomatic therapy(^{j})</td>
<td>...</td>
</tr>
<tr>
<td>Central or peripheral nervous system disease</td>
<td>Parenteral regimen(^{c})</td>
<td>14 (14–28)</td>
</tr>
<tr>
<td>Acrodermatitis chronica atrophicans</td>
<td>Oral regimen(^{c})</td>
<td>21 (14–28)</td>
</tr>
<tr>
<td>Post–Lyme disease syndrome</td>
<td>Consider and evaluate other potential causes of symptoms; if none is found, then administer symptomatic therapy(^{a})</td>
<td>...</td>
</tr>
</tbody>
</table>
# Antibiotics for Lyme Disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>Route</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>EM</td>
<td>PO</td>
<td>14-21 days</td>
</tr>
<tr>
<td>Meningitis</td>
<td>IV</td>
<td>14-28</td>
</tr>
<tr>
<td>Cranial nerve</td>
<td>PO</td>
<td>14-21</td>
</tr>
<tr>
<td>Arthritis</td>
<td>PO</td>
<td>28</td>
</tr>
<tr>
<td>CNS</td>
<td>IV</td>
<td>14-28</td>
</tr>
</tbody>
</table>
A Difficult Question

- *Can PFNP be treated orally?*
- IDSA guidelines stated the panel was divided on question of lumbar puncture for case of Lyme PFNP
- Some recommend for all patients
- Some reserve for those with strong clinical suggestion of CNS involvement
- Patients with clinical and laboratory evidence of CNS disease should receive regimens effective against meningitis
Prognosis

- Most patients respond very favorably to antibiotics
- Delayed diagnosis may result in greater morbidity
- PFNP – small risk of residual weakness
- CNS – long term cognitive sequelae described
- Arthritis – small risk of chronic arthritis
- Post-Lyme disease syndrome may occur
Straight from CDC
Concerning Post-Lyme Disease Syndrome

• Resources

  - "I don’t know what to believe"--This guide explains how scientists present and judge research and how you can ask questions about the scientific information presented to you. From the non-profit group, Sense about Science
  - "I’ve got nothing to lose"--A guide to understanding claims about cures and treatments from the non-profit group, Sense about Science
  - Pain management tools--From the American Chronic Pain Association log.
  - Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research--Committee on Advancing Pain Research, Care, and Education; Institute of Medicine.
  - Lyme disease clinical trials--A service of the U.S. National Institutes of Health.

Available at http://www.cdc.gov/lyme/postLDS/index.html
Reasons for Lack of Response to Appropriate Antibiotic Therapy

- Wrong diagnosis
- Coinfection
- Another coexisting condition (e.g. fibromyalgia)
- Permanent neurologic or joint damage from infection which has been cured
Preferred method for tick removal
Personal protective measures
Personal Protective Measures

- Light colored clothes
- Hat, long sleeves, long pants
- Tuck pants into socks
- Apply DEET to skin (may be toxic)
- Apply DEET to clothing
- Tick checks and tick removal
Prevention of Lyme Disease Following Tick Bites

- Personal protective measures
- Prompt removal of ticks
- Single dose doxycycline if:
  - tick definitely *I. scapularis*
  - prophylaxis can be started w/in 72 hr
  - local rate of infection in ticks ≥ 20%
  - doxycycline not contraindicated
- [tick engorgement, multiple deer tick attachments]
Educate your patients

**Ticks and Lyme Disease**

**How to prevent tick bites when golfing**

Ticks can spread disease, including Lyme disease. Protect yourself:

- Use insect repellent that contains 20 - 30% DEET.
- Wear clothing that has been treated with permethrin.
- Take a shower as soon as you can after coming indoors.
- Look for ticks on your body. Ticks can hide under the armpits, behind the knees, in the hair, and in the groin.
- Put your clothes in the dryer on high heat for 60 minutes to kill any remaining ticks.

**How to remove a tick**

1. If a tick is attached to you, use fine-tipped tweezers to grasp the tick at the surface of your skin.
2. Pull the tick straight up and out. Don’t twist or jerk the tick—this can cause the mouth parts to break off and stay in the skin. If this happens, remove the mouth parts with tweezers if you can. If not, leave them alone and let your skin heal.
3. Clean the bite and your hands with rubbing alcohol, an iodine scrub, or soapy water.
4. You may get a small bump or redness that goes away in 1-2 days, like a mosquito bite. This is not a sign that you have Lyme disease.

**Notes:** Do not put hot matches, nail polish, or petroleum jelly on the tick to try to make it pull away from your skin.

If you remove a tick quickly (within 24 hours) you can greatly reduce your chances of getting Lyme disease.

**Children and Lyme disease**

Although anyone can get Lyme disease, children spend a lot of time outdoors and are at particular risk.

Reasons to suspect that your child may have Lyme disease include:

- Your family lives in or has visited a region where Lyme disease is commonly found.
- You know or suspect that your child has been exposed to ticks.
- Your child is experiencing symptoms such as rash, fever, chills, fatigue, joint or muscle pain, or facial paralysis.

Children sometimes experience joint pain as their first, and possibly only, symptom of Lyme disease. If you suspect that your child may have Lyme disease, seek care promptly.

**What to expect from your child’s appointment**

If the doctor thinks that your child has Lyme disease based on symptoms and possible exposure, your child will most likely receive 2-4 weeks of antibiotics.

If your child’s symptoms are not clear-cut, the doctor may decide to have your child’s blood tested. Keep in mind that blood testing is more accurate the longer the child has been infected. A blood test for Lyme disease will not appear positive until 2-3 weeks after infection. Therefore, a doctor may order a late, second test if the first test was negative.

**Treatment of Lyme disease in children**

- A typical treatment for children less than 8-years-old would include oral amoxicillin three times daily for 2-4 weeks. Children who are allergic to amoxicillin would most likely receive cefuroxime axetil twice daily instead.
- A typical treatment for children over 8-years-old would include doxycycline twice daily for 2-4 weeks. Children who are allergic to tetracyclines would receive amoxicillin or cefuroxime axetil instead.

http://www.cdc.gov/lyme/toolkit/index.html
TICKBORNE DISEASES
OF THE
UNITED STATES

A Reference Manual
for Health Care Providers
Selected References