Lyme arthritis

Initially described as a distinct entity in 1975, after the identification of an epidemic of what appeared to be "juvenile rheumatoid arthritis" (pauciarthritides and monarthritides) in adults and children near Old Lyme, Connecticut (U.S.A.).
Lyme Disease History
The early elucidation of Lyme disease by Allen Steere and his colleagues at Yale is one of the most fascinating stories of clinical and epidemiologic investigation in recent years. This effort led to the description of a complex multisystem illness which, although existing in endemic pockets, has wide geographic dispersion and serves as a model for study of the manner in which an infecting organism can cause recurrent or persistent rheumatic inflammation.

In November 1975, a resident of Old Lyme, Connecticut, informed the Connecticut State Health Department that 12 children from that rural community of 5000 residents had been diagnosed to have juvenile rheumatoid arthritis. Almost concurrently, a second mother from Old Lyme informed physicians at the Yale Rheumatology Clinic that she, her husband, two of their children and several neighbors all had developed arthritis. A surveillance system organized by Drs Steere, Malawista and others revealed that 51 individuals (39 children and 12 adults) in three contiguous, rural communities had developed arthritis between July 1972 and May 1976. Most had recurrent brief attacks of pain and swelling (median 1 week) involving one to a few large joints, predominantly the knee. In 55%, the first attack of arthritis occurred between June and September, and 13 (25%) had noted a peculiar, expanding, erythematous skin lesion a median of 4 weeks prior to the onset of arthritis. One recalled being bitten by a tick at the site of the skin lesion. The skin lesion was suspected to be erythema chronicum migrans, described by Afzelius in 1910 and known to occur in Europe, where it had been associated with the bite of the sheep tick, Ixodes ricinus, and was suspected to be caused by infection with a transmissible agent.

In 1976, 32 more cases of this new entity, now called Lyme arthritis, were studied. In 24, the illness began with the skin lesions, now confirmed to be erythema chronicum migrans. (By convention, this skin lesion is now referred to as erythema migrans [EM].) Nineteen of these subsequently developed recurring attacks of monoarticular or oligoarticular arthritis a median of 4 weeks after appearance of the skin lesion, and eight individuals (30%) experienced arthritis without a preceding skin lesion. In addition, new features of the illness uncovered included self-limited cardiac conduction abnormalities and a variety of neurologic abnormalities, including Bell’s palsy, sensory radiculopathy and lymphocytic meningitis. Cardiac abnormalities had not been previously associated with EM but neurologic abnormalities were well documented. In 1922 Garin-Bujadoux had reported sensory radiculitis with meningeal signs following EM, and in 1944 Bannwarth had described patients with pain, paresthesia, Bell’s palsy and lymphocytic pleocytosis following a tick bite and EM. The new name Lyme disease was coined, recognizing the multisystem nature of the illness.

In subsequent reports, the cardiac conduction abnormalities and neurologic manifestations of Lyme disease were characterized more fully. Epidemiologic and serologic studies revealed an ixodid tick, I. scapularis, a newly described member of the I. ricinus complex in the region where cases of Lyme disease were occurring, strengthening the tick vector hypothesis. Antibiotic trials demonstrated that EM resolved faster and that later manifestations were usually prevented in individuals given penicillin or tetracycline, suggesting a bacterial agent transmitted by the tick vector. Subsequently, in 1982, Burgdorfer et al. reported the isolation of a spirochete from I. dammini ticks collected on Shelter Island, an area known to be endemic for Lyme disease. This organism, subsequently characterized as a Borrelia and named Borrelia burgdorferi, was cultured from I. scapularis ticks in Connecticut and from skin lesions, blood and meningitic cerebrospinal fluid of Lyme disease patients in Connecticut. It was also linked serologically to the disease. These data collectively established it definitively as the cause of Lyme disease.
Subsequent association with a distinct rash, erythema (chronicum) migrans, and other multisystem features of the syndrome led to the description of Lyme disease.
Lyme disease

A tick-borne infection with the spirochete Borrelia burgdorferi, causing systemic inflammatory lesions of the skin, joints, nervous system and/or heart.
Lyme disease

- Typical peak incidence in summer and fall months in geographic areas endemic for infected tick vectors.

- First clinical feature usually expanding skin lesions, erythema migrans, occurring at sites of tick bites.
Lyme disease

- Subsequent development of disseminated infection in most untreated patients resulting in a clinical picture which varies over time and, in some instances, chronic inflammation of joints, nervous system, heart or skin.

- Diagnosis based on clinical features, especially erythema migrans, and confirmatory serologic testing.

- **Antibiotic treatment highly effective.**
Tick infected with *Borrelia burgdorferi*

- Spirochete
- Salivary gland granules
- OspA
- OspC

Feeding tick

- *Borrelia burgdorferi*
- Salp15
- OspC

*NATURE MEDICINE, 2005*
OspC$^+$ bacteria, Salp15$^-$ tick: clearance in host
OspC\(^+\) bacteria, Salp15\(^+\) tick: survival in host

Spirochete

OspC

Salp15

Neutralizing antibody
Lyme disease

Early infection consists of localized erythema migrans (stage 1), followed within days or weeks by disseminated infection that affects the nervous system, heart, or joints in particular (stage 2) and subsequently, within weeks or months, by late or persistent infection (stage 3).
Malattia di Lyme

Precoce, localizzata

si manifesta da pochi giorni ad un mese dopo la puntura della zecca
Malattia di Lyme
Precoce, localizzata

- Astenia, malessere, letargia
- Cefalea
- Mialgie e/o artralgie
- Linfadenopatia
Malattia di Lyme
Precoce, localizzata
Eritema migrante
(nel 90% dei casi lesione isolata; lesioni multiple nel 10%)
Malattia di Lyme

Precoce, disseminata

si manifesta da pochi giorni
fino a 10 mesi dopo la puntura
Malattia di Lyme
(fase precoce, disseminata)

Cardite nell’8-10% dei pazienti non trattati
(turbe di conduzione)
Malattia di Lyme
(fase precoce, disseminata)

Compromissione neurologica nel
10-12% dei pazienti non trattati:
meningo-encefalite, neuropatia n. cranici -VII bilaterale-, neuropatie periferiche.
Malattia di Lyme
(fase precoce, disseminata)

Manifestazioni muscolo-scheletriche in circa il 50% dei pazienti non trattati:
poliartriti o poliartralgie, fibromialgia
Malattia di Lyme

Cronica/tardiva

si manifesta da mesi ad anni dopo la puntura
Malattia di Lyme
(fase tardiva, cronica)

Manifestazioni muscoloscheletriche:
in circa il 50% dei casi non trattati sviluppo di una poliartrite migrante.
In circa il 10% dei casi monoartrite, specie alle ginocchia.

Fibromialgia.
Malattia di Lyme
(fase tardiva, cronica)

Malattia neurologica

Cronica, spesso subdola
(encefalopatia o neuropatia periferica; deterioramento cognitivo)
Acrodermatitis Chronicum Atrophicans

Usually occurs on the acral portion of an extremity and is characterized by violaceous discoloration and swelling of involved skin, often at a site where EM occurred years earlier. The lesion eventually becomes atrophic. It is thought to result from local persistence of B. burgdorferi, which has been isolated from a lesion 10 years after onset.
Centers for Disease Control and Prevention Criteria for Lyme Disease

Presence of EM \textbf{OR} Cases with at least one late manifestation plus laboratory confirmation of infection.

The late manifestations include any of the following when an alternate explanation is not found:

- \textbf{Musculoskeletal system} – Recurrent brief attacks of objective joint swelling in one or a few joints, sometimes followed by chronic arthritis in one or a few joints. Manifestations not considered as criteria for diagnosis include chronic progressive arthritis not preceded by brief attacks and chronic symmetrical polyarthritis. Additionally, arthralgias, myalgias, or fibromyalgia syndromes alone are \textbf{not accepted} as criteria for musculoskeletal involvement.

- \textbf{Nervous system} – Lymphocytic meningitis, cranial neuritis, particularly facial palsy (may be bilateral), radiculoneuropathy or, rarely, encephalomyelitis alone or in combination. Encephalomyelitis must be confirmed by showing antibody production against B. burgdorferi in the cerebrospinal fluid (CSF), which is demonstrated by a higher titer of antibody in CSF in serum. Headache, fatigue, paresthesias, or mild stiff neck alone are \textbf{not accepted} as criteria for neurologic involvement.

- \textbf{Cardiovascular} – Acute onset, high grade (2nd or 3rd degree) atrioventricular conduction defects that resolve in days to weeks and are sometime associated with myocarditis. Palpitations, bradycardia, bundle branch block, or myocarditis alone are \textbf{not accepted} as criteria for cardiovascular involvement.
Erythema migrans, observed by a physician. This skin lesion expands slowly over a period of days or weeks to form a large, round lesion, often with central clearing. To be counted for surveillance purposes, a solitary lesion must reach a size of at least 5 cm.

At least one subsequent manifestation and laboratory evidence of infection

Nervous system: Lymphocytic meningitis, cranial neuritis, radiculoneuropathy, or rarely, encephalomyelitis, alone or in combination. For encephalomyelitis to be counted for surveillance purposes, there must be evidence in cerebrospinal fluid of the intrathecal production of antibody against *Borrelia burgdorferi*.

Cardiovascular system: Acute-onset, high-grade (2nd- or 3rd-degree) atrioventricular conduction defects that resolve in days or weeks and are sometimes associated with myocarditis.

Musculoskeletal system: Recurrent, brief attacks (lasting weeks to months) of objectively confirmed joint swelling in one or a few joints, sometimes followed by chronic arthritis in one or a few joints.

Laboratory evidence: Isolation of *B. burgdorferi* from tissue or body fluid or detection of diagnostic levels of antibody against the spirochete by the two-test approach of enzyme-linked immunosorbent assay and Western blotting, interpreted according to the criteria of the Centers for Disease Control and Prevention and the Association of State and Territorial Public Health Laboratory Directors.

*Adapted from recommendations made by the Centers for Disease Control and Prevention.*

†In a person with acute disease of less than one month’s duration, IgM and IgG antibody responses should be measured in serum samples obtained within one month of the onset of illness. A WSTavidia for Lyme
The diagnosis of Lyme disease is usually based on:

✓ the recognition of the characteristic clinical findings,

✓ a history of exposure in an area where the disease is endemic,

and except in patients with erythema migrans,

✓ an antibody response to *B. burgdorferi* by enzyme-linked immunosorbent assay (ELISA) and Western blotting.
The Serologic Response in Lyme Disease

Antibody titer

Normal range

Time after onset of symptoms

IgM — IgG

Weeks

Years
<table>
<thead>
<tr>
<th>Time of infection</th>
<th>Isotype</th>
<th>Bands to be considered</th>
</tr>
</thead>
<tbody>
<tr>
<td>First few weeks</td>
<td>IgM</td>
<td>Two of the following: ospC (23), 39, 41</td>
</tr>
<tr>
<td>After first few weeks</td>
<td>IgG</td>
<td>Five of the following: 18, 21, 28, 30, 39, 41, 45, 58, 66, 93</td>
</tr>
</tbody>
</table>

**Western blot diagnosis of Lyme disease**  Criteria for positive western blot (immunoblot) analysis in the serologic confirmation of infection with *Borrelia burgdorferi* (Lyme disease). Criteria derived from Dressler, F, Whalen, JA, Reinhardt BN, Steere AC, J Infect Dis 1993; 167:392. *Alternate criteria for IgM reactivity, proposed by a Centers for Disease Control and Prevention conference. Other points noted at that conference were the need for standardization of the antigen preparation and techniques used.*
<table>
<thead>
<tr>
<th>Suggested Antibiotic Regimens for Lyme Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early disease</strong></td>
</tr>
<tr>
<td>• Doxycycline, 100mg p.o., twice daily for 21 days, or</td>
</tr>
<tr>
<td>• Amoxicillin (with or without probenecid) 500mg, three times daily for 21 days, or</td>
</tr>
<tr>
<td>• Erythromycin, 250-500mg p.o., four times daily for 21 days, or</td>
</tr>
<tr>
<td>• Azithromycin 500mg qd for 7 days, or</td>
</tr>
<tr>
<td>• Cefuroxime axetil, 500mg p.o., twice daily for 21 days.</td>
</tr>
<tr>
<td>Shorter courses may suffice for localized early disease.</td>
</tr>
<tr>
<td>Erithromycin and azithromycin less effective than other choices.</td>
</tr>
<tr>
<td><strong>Lyme arthritis</strong></td>
</tr>
<tr>
<td><strong>Initial treatment:</strong></td>
</tr>
<tr>
<td>• Doxycycline, 100mg p.o., twice daily for 30 days, or</td>
</tr>
<tr>
<td>• Amoxicillin and probenecid, 500mg each, p.o., four times daily for 30 days.</td>
</tr>
<tr>
<td><strong>If initial treatment fails:</strong></td>
</tr>
<tr>
<td>• Penicillin G, 20 x 10^6 IU i.v., daily in divided doses for 14 days, or</td>
</tr>
<tr>
<td>• Ceftriaxone sodium, 2g i.v., daily for 14 days.</td>
</tr>
<tr>
<td><strong>Neurologic manifestations</strong></td>
</tr>
<tr>
<td><strong>For facial nerve paralysis alone:</strong></td>
</tr>
<tr>
<td>• Doxycycline, 100mg p.o., twice daily for 21-30 days, or</td>
</tr>
<tr>
<td>• Amoxicillin, 500mg p.o., three times daily for 21-30 days.</td>
</tr>
<tr>
<td><strong>Additional signs</strong></td>
</tr>
<tr>
<td>(e.g. Lyme meningitis, radiculopathy, encephalitis)</td>
</tr>
<tr>
<td>• Ceftriaxone, 2g i.v., daily for 30 days, or</td>
</tr>
<tr>
<td>• Penicillin G, 20 x 10^6 IU i.v., daily in divided doses for 30 days.</td>
</tr>
<tr>
<td><strong>Possible alternatives:</strong></td>
</tr>
<tr>
<td>• Cefotaxime sodium, 2g i.v., q8h for 30 days, or</td>
</tr>
<tr>
<td>• Doxycycline, 100mg p.o., q12h for 14-30 days, or</td>
</tr>
<tr>
<td>• Chloramphenicol, 1g i.v., q6h for 14-30 days.</td>
</tr>
<tr>
<td><strong>Lyme carditis</strong></td>
</tr>
<tr>
<td>• Ceftriaxone, 2g i.v., daily for 14 days, or</td>
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<td>• Penicillin G, 20 x 10^6 IU i.v., daily in divided doses for 14 days.</td>
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<td><strong>Possible alternatives:</strong></td>
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<tr>
<td>• Doxycycline, 100mg p.o., twice daily for 21 days, or</td>
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<tr>
<td>• Amoxicillin, 500mg p.o., three times daily for 21 days.</td>
</tr>
<tr>
<td><strong>During pregnancy</strong></td>
</tr>
<tr>
<td><strong>Localized, early disease:</strong></td>
</tr>
<tr>
<td>• Amoxicillin, 500mg p.o., three times daily for 21 days.</td>
</tr>
<tr>
<td><strong>Other manifestations:</strong></td>
</tr>
<tr>
<td>• Penicillin G, 20 x 10^6 IU i.v., daily in divided doses for 14-30 days, or</td>
</tr>
<tr>
<td>• Ceftriaxone, 2g, daily for 14-30 days.</td>
</tr>
</tbody>
</table>
Should *I. scapularis* tick bites be treated with antibiotic prophylaxis?

In studies, the frequency of Lyme disease after a recognized tick bite has been only about 1%, perhaps because the tick must usually be attached for at least 24 hours for transmission to occur.

Thus, if an attached tick is removed quickly, no other treatment is usually necessary.

However, a single 200-mg dose of doxycycline effectively prevents Lyme disease when given within 72 hours after the tick bite occurs.