Harvard Rheumatology Course

Curbside Consult: Lyme Disease

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Allen C. Steere, MD

Division of Rheumatology, Allergy and Immunology
Massachusetts General Hospital
Harvard Medical School

Conflict of Interest Review

Served as a consultant for Roche Diagnostics, Zeus, Pfizer, and Viramed

Objectives of Presentation

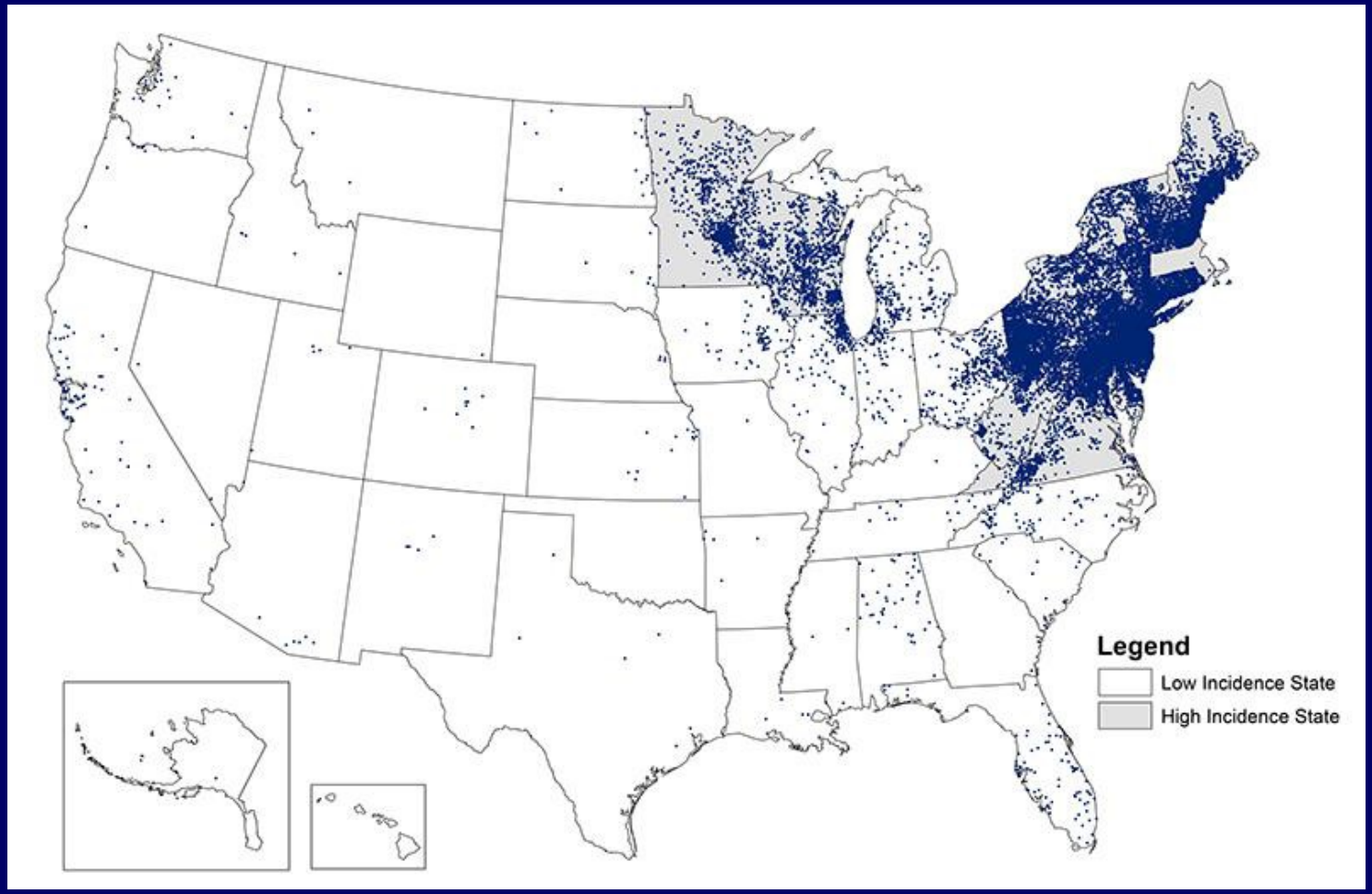
Key Learning Points –

Upon completion of this lecture, participants will be able to recognize the presentations of Lyme arthritis, interpret serologic results, and apply a treatment algorithm for management.

Next Best Steps –

Recognize that the post-infectious syndromes that may follow Lyme disease are still being defined and require a different approach to treatment.

Reported Cases of Lyme Disease – United States, 2019



~400,000 estimated cases in the USA each summer.

Comparison of OspC Types from EM Patients in New England, New York, and Wisconsin

OspC Type	New Engl * (N = 91)	New York** (N = 291)	Wisconsin* (N = 65)
A	36%	16%	3%
B	14%	13%	3%
H	5%	4%	18%
I	7%	7%	3%
K	21%	30%	6%

Of 23 OspC types now identified, 5 are more often associated with disseminated infection. OspC type A is particularly virulent.

*Jones KL, J Clin Micro 2006;44:4407-13**Hanincova K et al. PLOS one 2013:8:e73066

Tick-Borne Agents Transmitted by the Deer Tick

Deer tick (*Ixodes scapularis*)

- *Borrelia burgdorferi* – OspC type A strains are particularly inflammatory and more often associated with severe disease.
- *Babesia microti* – a red-cell parasite, a malaria-like illness.
- *Anaplasma phagocytophilum* – A ricksettsia-like organism that infects granulocytes, a flu-like illness
- *Borrelia miyamotoi* – a relapsing fever borrelia; a flu-like illness, but can cause neurologic involvement in immunosuppressed patients
- *Borrelia mayonii* – found only in the upper Mid-west
- Powassan (deer tick) encephalitis virus – a neurotropic virus Can be fatal and can cause permanent neurologic sequelae.

Clinical Picture of Lyme Disease

Stage 1: Early localized (days to weeks)

Erythema migrans: often accompanied by flu-like symptoms

Stage 2: Early disseminated (weeks to months)

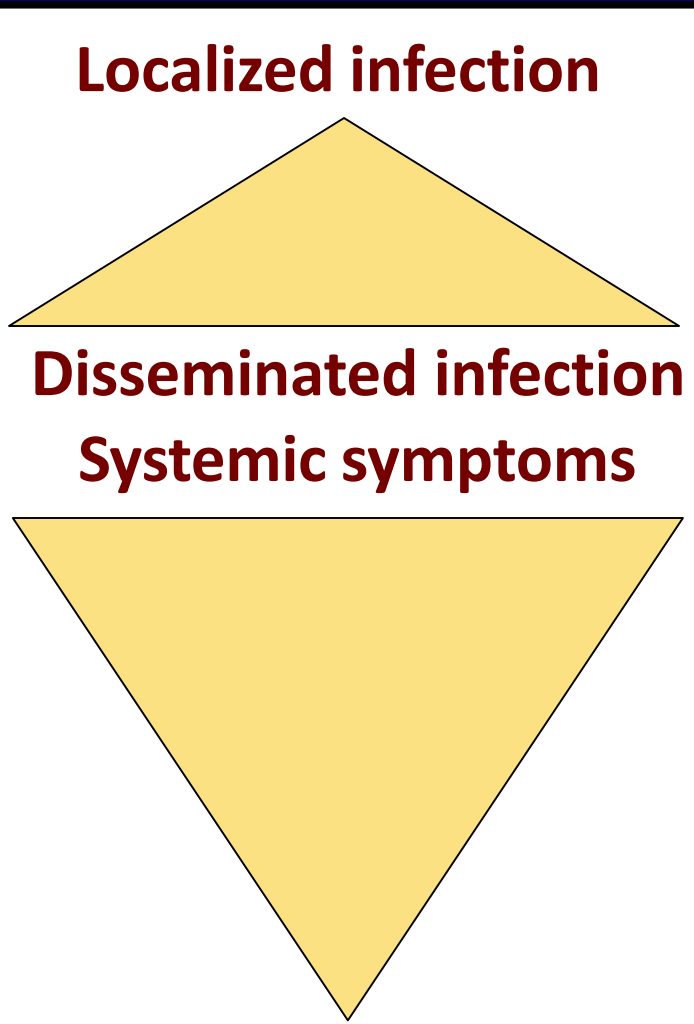
Acute Lyme neuroborreliosis: acute neurologic involvement, lymphocytic meningitis, cranial neuritis, and sensory or motor radiculneuropathy

Lyme carditis: Atrioventricular block

Stage 3: Late (months to years)

Lyme arthritis: Arthritis in one or a few joints, most commonly the knee. Usually without systemic symptoms

Late Lyme neuroborreliosis: Rarely, subtle encephalopathy or sensory polyneuropathy



Natural History of Lyme Arthritis

- Arthritis began 4 days to 2 years (mean, 6 months) after EM skin lesions
- Arthritis characterized by intermittent or persistent attacks of joint swelling and pain, primarily in a few large joints, especially the knee, during a period of several years.
- Particularly in earlier episodes, other large or small joints, the TMJ, or bursa or tendons were sometimes affected.
- Knee joints were often very swollen, but not particularly painful and ruptured Baker's cysts were common.
- By the time arthritis was present, systemic manifestations (fever or other constitutional symptoms) were uncommon.

Steere et al., *Ann Intern Med* 1987;107:725-31

Diagnosis of Lyme Disease*

- Recognition of a characteristic clinical picture
- Exposure in an endemic area
- Positive antibody response to *B. burgdorferi* determined by a two-test approach of ELISA and Western blot, interpreted according to the criteria of the Centers for Disease Control.†

First 30 days of symptoms: two of the following three IgM bands,
23, 39, 41-kD
At any time in the illness: five of the following ten IgG bands,
18,23,28,30,39,41,45,58,66,93-kD

Alternate two-test approach of two EIAs*,
most commonly a whole cell sonicate followed by VlsE test

† CDC, Recommendations for test performance and interpretation. *MMWR* 1995;44:590

*CDC, Mead P; MMWR https://doi.org/10.15585/mmwr.mm6832a4. Q

Whole Cell SonicateELISA and Western Blot in Patients with Lyme Disease*

	No. of Patients Positive (%) IgM or IgG WCS + WB
Lyme Disease	
Erythema migrans (N=76)	
Acute	22(29)
Convalescent	49(64)
Early disseminated infection (N=13)	
Carditis or acute neuro	13(100)
Late infection (N=31)	
Arthritis or chronic neuro	31(100)
Post-Lyme disease symptoms (N=14)	10(71)
Past LD; another current illness (N=14)	11(79)
Non Lyme disease (N=75)	0(0)
Geographic control subjects (N=86)	2(2)
Non-geographic control subjects (N=50)	0(0)

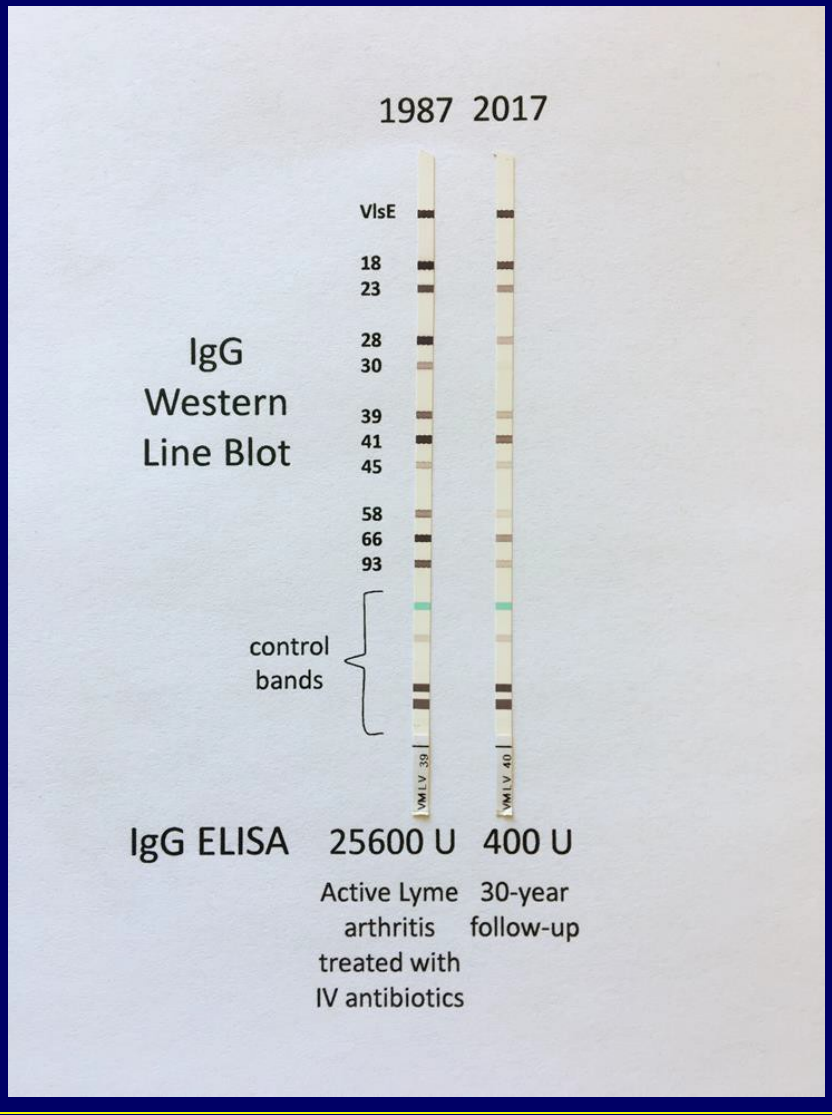
*Steere et al, *Clin Infect Dis* 2008;47:188-95

Comparison of Standard 2-tiered ELISA and Western Blot with 2-EIAs (WCS and C6-peptide) for Serodiagnosis of Lyme Disease*

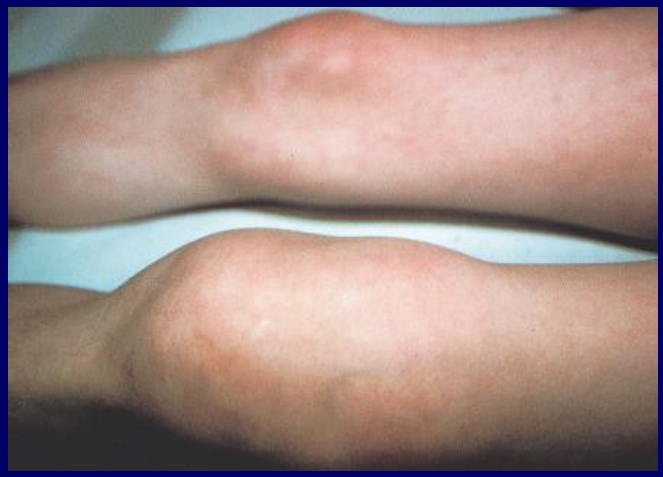
	Standard 2-tiered algorithm[d]	2-EIA algorithm[e]
Patients with Lyme disease (N = 91)		
Stage 1: Erythema migrans (n = 63)		
Active phase	17 (27)	23 (37)
Convalescent phase	36 (57)	56 (89)
Stage 2: Acute neuritis or carditis (n = 10)	4 (40)	10 (100)
Stage 3: Arthritis or late neuritis (n = 18)	18 (100)	18 (100)
Symptomatic control subjects (N = 54)[d]	0 (0)	0 (0)
Healthy control subjects (N = 1246)		
Connecticut or Rhode Island field sites (N = 66)	1 (2)	1 (2)
Boston blood donors (N = 1080)	6 (1)	6 (1)
New Zealand blood donors (N = 100)	0 (0)	0 (0)

*Branda et al., *Clin Infect Dis* 2011;53:541-7.

After antibiotic therapy, the amount of antibody declines, but the Western blot does not change much.



Antibiotic Therapy for Lyme Arthritis*



Initial Treatment

- Oral doxycycline, 100mg twice daily for 30 days
- Oral amoxillin, 500mg three times daily for 30 days

Mild persistent arthritis after 30 days of therapy

→ Repeat oral antibiotic regimen for another 30 days

Moderate to severe persistent arthritis after 30 days of therapy

→
- IV ceftriaxone, 2g daily
- IV penicillin G, 20 million U in 6 divided doses daily, in each instance, for 30 days

Mild persistent arthritis → NSAIDs, Intra-articular steroids

Proliferative synovitis → Methotrexate, TNF Inhibitor

* Arvikar SL and Steere AC. *Infect Dis Clin N Amer* 2015;29:269-80.

Patient 1

In late July, a 60-year-old woman suddenly developed marked swelling of the right knee. She had no other symptoms. She lives in a highly endemic area for Lyme disease. Her mother, husband, and dog have had the infection.

On examination, the right knee was markedly swollen as was the calf and ankle. She had only 15 degrees of flexion. ESR 58, CRP 139, IgG *Bb* ELISA 3,200 U, IgG WB, 18,23,28,30,39,41,45,58,66,93-kD bands
JF WBC 19,750 cells/mm3, 81% polys. PCR test – positive for *Bb* DNA.

Diagnosis: Lyme arthritis
Treatment: doxycycline 100 mg twice daily for 30 days. Crutch walking

In follow-up 30 days later, 50% improvement in joint and calf swelling.
ESR 17, CRP 1.4, IgG *Bb* ELISA 12,800 U

Patient 1, part 2

She was treated with a second one-month course of doxycycline.

In follow-up 30 days later, 2 months after presentation, the right knee showed only a small bulge sign, mild bogginess of the synovium, and mild swelling of a bursa around the knee. She still lacked about 10-20 degrees of flexion and had moderate quad atrophy. ESR 2, CRP 0.2, IgG *Bb* ELISA 25,600 U

Treatment: bike riding, and leg lifts with 5 lb. weights
No more medication prescribed

In follow-up 2 months later, the right knee still showed a very small bulge sign. She lacked about 10 degrees of flexion and still has moderate quad atrophy. ESR 2, CRP 0.2, IgG *Bb* ELISA 3,200U.

Patient 2

In July 2017, a 17-year-old young man in the Philadelphia area had marked swelling of the right knee. He had no previous symptoms. Within 1 week, Lyme arthritis was diagnosed. He received a one-month course of oral doxycycline, but the knee did not improve.

In August 2017, he received his second, 1-month course of oral doxycycline, but the knee did not improve.

Over an 8-month period, he had 3 intra-articular steroid injections, but each one helped for only 1-2 weeks. He tried ibuprofen, which provided mild pain relief, but the knee remained markedly swollen.

In April 2018, hydroxychloroquine and naprosyn were begun, which did not help. He received a 4th intra-articular steroid injection, which again only helped for several weeks.

In August 2018, he started methotrexate. He took the medication for 3 months, but did not find it helpful. For the past 5 months, he has taken no medication. He says that his knee is basically unchanged despite all therapies that he has received.

Patient 2, Part 2

He was evaluated at MGH in April 2019. He reported only right knee swelling and pain. He had no associated symptoms. The right knee interfered with running and other athletic activities.

The right knee was moderately swollen and mildly warm. He lacked about 10 degrees of flexion and has mild quadriceps atrophy.

Lab data: WBC 11,410, Hct 45.2, Plts 253,000, ESR 5, CRP 20.4

Antibody to *B. burgdorferi*

	ELISA	Western blot
IgM	Negative	
IgG	25,600 U	18,23,28,39,41,56,68,66,93-kD and VlsE

The right knee was aspirated of 15 ml of cloudy yellow fluid
White count 42,543, 89% polys, 5% lymphs, and 6% monos

Ultrasound: synovitis, tenosynovitis, moderate fluid, and marked calcification of hamstring tendons.

Conclusion: the patient is still infected with B. burgdorferi

Patient 2, Part 3

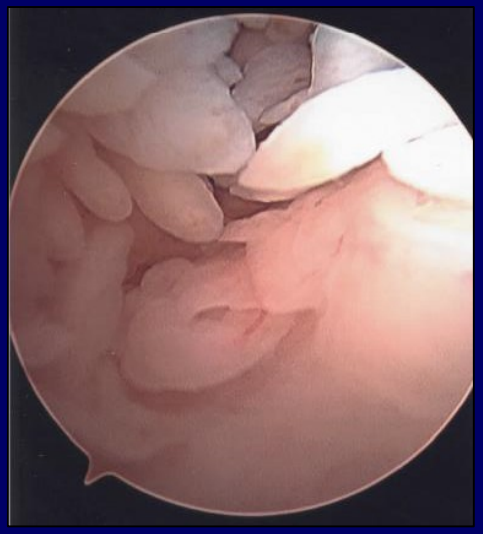
June 2019 – The patient received IV ceftriaxone, 2g daily for 28 days. He began to have improvement in his right knee swelling within 1 week after starting the medication.

On July 19, 2019 – The right knee showed only a bulge sign. He had complete range of motion of the knee without pain. There was moderate quad atrophy.

Lab data – WBC 6,300, ESR 2, CRP 0.4
IgG Lyme titer – 3,200 U

Over the next several months, he had complete resolution of knee swelling and return to running and other athletic activities.

Post-Infectious (Antibiotic-refractory) Lyme Arthritis*



- In refractory patients, synovitis seems to change after spirochetal killing with antibiotics, and massive synovial proliferation develops.

- In synovial tissue, obtained in the post-antibiotic period, culture and PCR results for *B. burgdorferi* have been uniformly negative.*

- The basic pathogenetic feature of post-infectious LA is the development of an excessive, dysregulated proinflammatory immune response during the infection, characterized by exceptionally high levels of IFN-ψ and inadequate levels of IL-10, that persists in the post-infectious period.

The consequences of this immune response in Lyme synovia include vascular damage, autoimmune and cytotoxic processes, and fibroblast proliferation.

*Lochhead RB et al, Lyme arthritis, linking infection, inflammation and autoimmunity, Nat Rev Rheum, Aug, 2021

Patient 3

In March 2018, a 62-year-old man developed fever and right knee pain and swelling. He had an intra-articular steroid injection. Two weeks later, the left calf and knee became swollen, which was treated with an intra-articular steroid injection. In April, a PCR test for *Bb* DNA on JF was positive. A WB showed 10/10 IgG bands. He was treated with 28 days of doxycycline. This had no effect. The dose of doxycycline was doubled for one month, but no improvement. He was treated for one month with Zithromax and malarone, the treatment for babesiosis, though tests were negative for that infection. He had no improvement. More steroid injections were given without benefit.

In June, treatment was started with IV ceftriaxone, which seemed to help. However, he developed skin ulcers on the feet and oral ulcers, and the antibiotic was stopped after 10 days of therapy. He was treated with oral ceftin, malarone, and duexis for 5 months with no benefit. The PCR test on JF for *Bb*DNA remained positive.

Patient 3, part 2

In Nov. 2018, at MGH, both knees were moderately swollen and warm. Lyme IgG antibody 25,600 with 10/10 IgG bands. JF WBC 6,178 with 68% polys, *Bb*PCR Neg. ESR 48, CRP 34.5. Decided to try methotrexate 15 then 20 mg weekly. GI upset, no response.

The step of IV antibiotics had been truncated because of a possible incipient Stevens-Johnson reaction. Allergy recommendation: avoid any beta-lactam antibiotic. In March 2019, we decided to treat with IV doxycycline, 100 mg bid for 30 days. He had remarkable improvement with about 90% improvement in knee swelling and pain bilaterally. ESR 11, CRP 1.9. US still showed inflammation in right knee, but minimally so in the left knee. Within 2 mos., his Lyme antibody titer began to decline from 25,600 U to 3,200 U.

Two weeks after completing IV doxy, the right elbow became swollen. ESR 27, CRP 6.6. MRI showed inflammatory synovitis. He was treated with Enbrel 50 mg weekly.

Patient 3, part 3

On Enbrel, his elbow improved rapidly. Two months later, in May 2019, exam showed only a small bulge sign and slight warmth in the left knee, the right knee and elbow were normal. ESR 8, CRP 0.6.

He started a quad strengthening exercise program. He biked 15 miles, 4 times a week. He is playing golf again.

He reported the development of pain over the left lateral knee and IT band pain intermittently with exercise. US showed focal left lateral compartment synovial thickening between the IT band and the femoral condyle, causing IT band friction. He received a US guided steroid injection at the site of synovitis with resolution of the pain.

Enbrel was continued for another 5 months for a total of 8 months of Enbrel therapy. He has remained well.

Systemic Rheumatic Autoimmune Diseases After Lyme Disease

•Of 30 patients, 15 developed new-onset rheumatoid arthritis, 13 developed psoriatic arthritis, and 2 developed peripheral spondyloarthropathy a median of 4 months after early or late manifestations of Lyme disease.

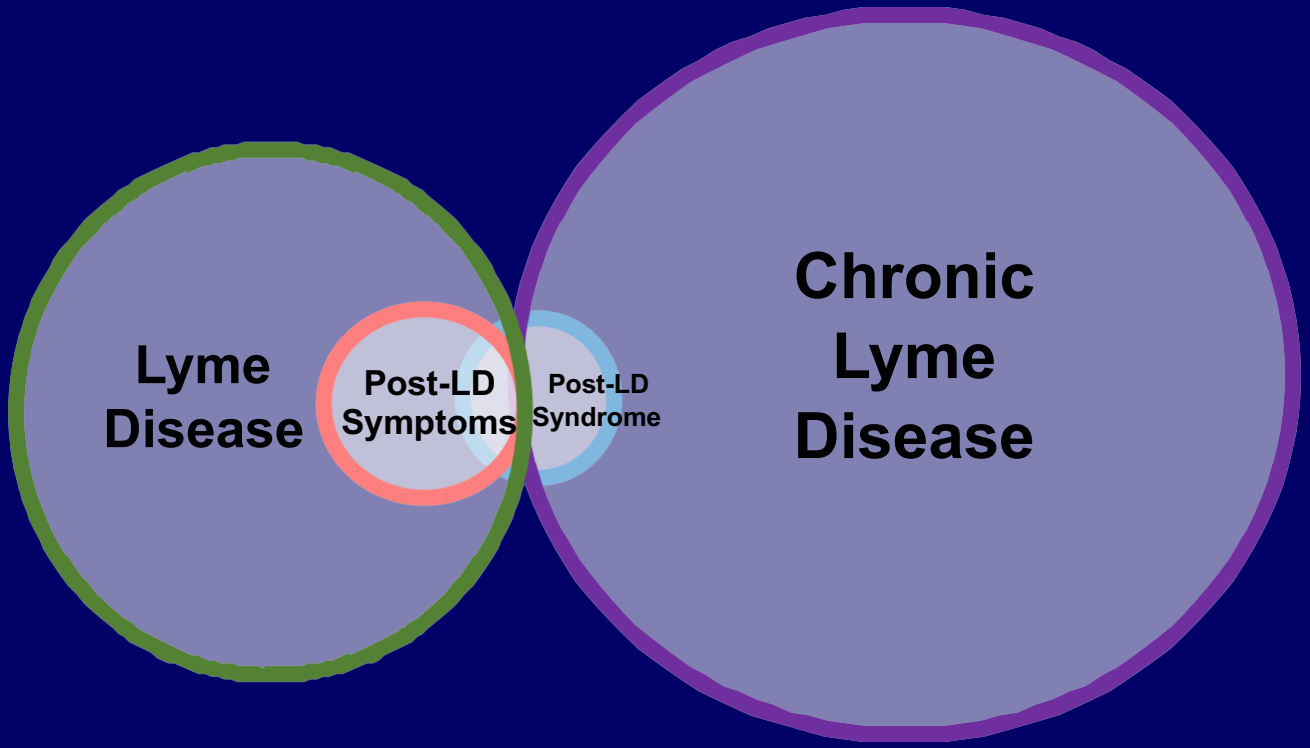
•In 25 of the 30 patients (81%), the rheumatic disease followed an early manifestation of Lyme disease, most commonly antibiotic-treated erythema migrans. The patients were often thought to have Lyme arthritis and were treated with antibiotics, sometimes for months or years, without benefit and in some cases, with considerable harm.

•They had significantly lower antibody titers to *B. burgdorferi* than patients with Lyme arthritis (mean titer 1:400 versus 1:16,000), and a lower frequency of Lyme-associated autoantibodies.

•They responded to therapy with disease modifying anti-rheumatic drugs (DMARDs), the standard of care for these diseases.

Arvikar et al., *Arthritis Rheumatol* 2017;69:194-202

Post-Treatment Lyme Disease Syndrome



Aucott JN, Post-treatment Lyme Disease Syndrome, *Inf Dis Clin North Am* 2015;29:309-23

Case 4: *58 yo M with HA, brain fog and paresthesia after Bell's palsy*

- **History:** In August 2016, the patient had onset of back pain, leg pain, and paresthesia. Stopped his statin and started prednisone which helped initially, then given medrol. In 9/16 he noted rash suggestive of EM and then R facial droop. Lyme serology positive (7 IgG, 3 IgM). He was then started on doxycycline with improvement but had continued HA. Prescribed IV ceftriaxone x 1 month.

- 6 months later, continued to have persistent HA, brain fog, foot pain. Did have some improvement with topiramate and duloxetine. Participated in functional restoration program with OT. He remains with neurocognitive symptoms and has had to stop working as a lawyer. He has difficulty with simple tasks such as following instructions for a recipe or driving a car if someone is talking to him.

- **Physical Exam:** no synovitis or neurologic deficit

- **Data:** CRP 4.8, ESR 14, Neg RF, CCP, CSF 0 WBC, No oligoclonal bands, MRI resolution of prior facial nerve enhancement. **Neuropsych testing: significant cognitive impairment relative to potential.**

- **Ddx:**
    - CNS Lyme infection (normal objective data)
    - Other headache syndrome
    - ✓ PTLDS

Post-Treatment Lyme Disease Syndrome (PTLDS)

- ~10% of patients may have persistent, or subsequently develop, non-specific joint and muscle pain, fatigue, neurocognitive symptoms after Lyme disease
  - Referred to as "syndrome" if functional impairment
  - No objective inflammation/abnormalities

- Differential Diagnosis
  - **No diagnostic test**
  - Ddx other entities—fibromyalgia, CFS/myalgic encephalomyelitis, rheumatic disease, infections
  - May be ascribed to patients without history of Lyme disease,

  - No approved treatment
  - Symptomatic treatment
  - Antibiotic trials have not shown benefit, but patients/advocacy groups may request prolonged treatments
  - Unproven therapies marketed to patients

"Objective laboratory or imaging findings should not be used as the only measure or assessment of a patient's well-being; lack of laboratory or imaging abnormalities does not invalidate the existence, severity, or importance of a patient's symptoms or conditions."

https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-index.html

Lantos PM, Clin Inf Dis, 2015

Table 1. Examples of Alternative Medical Therapies Marketed to Patients for the Treatment of Lyme Disease

Categories of Therapy	Examples
Oxygen	Hyperbaric oxygen Hydrogen peroxide Ozone
Energy and radiation	Ultraviolet light Photon therapy "Cold" lasers Saunas and steam rooms "Rife" therapy (electromagnetic frequency treatments) Magnets
Metal/chelation	Mercury chelation and removal Dimercaptosuccinic acid (DMSA) 2,3-Dimercapto-1-propanesulfonic acid (DMPS) Alpha lipoic acid (ALA) Ethylene diamine tetraacetic acid (EDTA) Removal of dental amalgam Colloidal silver Bismuth
Nutritional supplements	Vitamins C and B12 Herbs Garlic, cilantro, Chlorella, Sarsaparilla, Andrographis, Turmeric, Olive leaf, Cat's claw Burnt mugwort (moxibustion) Glutathione Fish oil Magnesium Salt
Biological and pharmacologic	Urotherapy (urine ingestion) Enemas Bee venom Hormonal therapy Dihidroepiandrostenedione, Pregnenolone, Cortisone, Hydrocortisone Synthetic thyroid hormone Lithium orotate Olmesartan Cholestyramine Naltrexone Sodium chlorite (bleach) Intravenous immune globulin (IVIG) Apheresis Stem cell transplantation

Passive Transfer of Fibromyalgia Symptoms from Patients to Mice*

- Transfer of IgG from 44 fibromyalgia patients produced sensory hypersensitivity in mice by sensitizing nociceptive neurons.
- IgG from patients labeled mouse satellite glial cells and neurons in dorsal root ganglia, but did not cause apparent damage to these cells, rather it appeared to change their metabolism. There was also thinning of small sensory fibers in skin.
- IgG-depleted serum from fibromyalgia patients or sera from healthy subjects had no effect.
- These results suggest that fibromyalgia patients may have autoreactive IgG antibodies against certain neural components. However, the authors were not able to identify specific neural autoantigens in patients' samples.

*Goebel et al. *J Clin Invest* 2021;131:e144201

Sumary of Key Points

OspC type A strains of *B. burgdorferi* are more inflammatory; they cause more severe disease, and they are more often associated with post-antibiotic Lyme arthritis.

Although the amount of antibody to *B. burgdorferi* declines after successful antibiotic treatment of the infection, the Western blot, a non-quantitative test does not change much after treatment and remains positive for years.

Most patients with Lyme arthritis respond to treatment with 1-2 months of oral doxycycline, but some do not, and require IV antibiotic therapy for successful treatment of the infection.

Several post-infectious phenomena may follow Lyme disease, including post-antibiotic Lyme arthritis or the development of another type of inflammatory arthritis, or post-treatment Lyme disease syndrome (PTLDS), which is similar to fibromyalgia.

Lyme, Connecticut

For overview: Steere et al. Lyme borreliosis, Nature Rev Dis Primers, Dec 2016

Thank you for your attention.