Date: Tuesday, October 29, 2013, 7:00 pm – 8:45 pm

Topic: LYME DISEASE – HISTORY AND CURRENT CONTROVERSIES

Speaker: Richard A. Jacobs, MD, PhD, Emeritus Clinical Professor of Medicine, Division of Infectious Diseases

Biography:

Richard Jacobs, MD, PhD is Emeritus Clinical Professor of Medicine in the Division of Infectious Diseases at UCSF. After receiving his MD and PhD degrees from Washington University in St. Louis, he came to UCSF to pursue training in Internal Medicine. During his residency training he developed an intense interest in infectious diseases and was one of the first physicians to be trained in that specialty at UCSF. After a brief period in private practice in infectious diseases he joined the full time faculty at UCSF where he continues to see patients and teach on a part time basis. He is the proud recipient of the Vincent G. Pons Award in Clinical Infectious Disease and is an inaugural member of The Council of Master Clinicians.

Bibliography:


Lyme Disease—History and Current Controversies
Richard A. Jacobs, MD, PhD

Outline
• History of Lyme disease
  – How the "new" disease was discovered
  – How the cause or the etiology of the disease was discovered
• Clinical manifestations
• Diagnosis
• Therapy
• Prevention
  – Vaccine and lessons learned
• Controversies

Definition
Lyme disease is a bacterial infection caused by the spirochete Borrelia burgdorferi in the US and Borrelia afzelii, and Borrelia garinii in Europe and Asia and is transmitted to humans by the bite of infected Ixodes ricinus complex tick. The clinical manifestations can be complex but affect primarily the skin, joints, nervous system and heart.
What the @#%&*...... Are you talking about

Definition
• Lyme disease is a bacterial infection

Organisms Seen in Infectious Diseases
• Bacteria
  – Single celled organisms that divide by fission
  – Can exist anywhere
  – Respond to antibiotic therapy
• Viruses
  – Smaller organisms
  – Live within host cells
  – Do not respond to antibiotic therapy
• Yeast/Molds
• Parasites

Definition
• Lyme disease is a bacterial infection caused by the spirochete Borrelia burgdorferi in the US and Borrelia afzelii, and Borrelia garinii in Europe and Asia
Types of Bacteria

- Gram positive—S. aureus
- Gram negative—E. coli
- Acid Fast—Tuberculosis
- Spirochetes—Lyme disease and Syphilis

Definition

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“Tick Biology 101”

- Hard ticks (over 700 species)
  - Ixodes ricinus complex
    - Different geographic distributions
      - Northeastern and upper midwestern states
        - Ixodes scapularis (also called Ixodes dammini)
      - Western states—Ixodes pacificus
      - Europe—Ixodes ricinus
      - Asia—Ixodes persulcatus
- Soft ticks (over 150 species)

“Tick Biology 101” (continued)

- Three stages:
  - Larval—feeds from August to September on white-footed mouse
  - Nymphal★★—feeds from May through July on white-footed mouse
  - Adult—feeds on larger mammals, especially deer in the spring and fall

★★ nymph primarily responsible for disease transmission

“Summer Flu”
Tick Biology (continued)

Engorged Tick

Tick Biology (continued)
Definition

Lyme disease is a bacterial infection caused by the spirochete Borrelia burgdorferi (B. burgdorferi) in the US and Borrelia afzelii (B. afzelii) and Borrelia garinii (B. garinii) in Europe and Asia and is transmitted to humans by the bite of infected Ixodes rinsicus complex tick complex.

The clinical manifestations can be complex but affect primarily the skin, joints, nervous system and heart.

History of Lyme Disease

• 1909 a Swedish dermatologist, Arvid Afzelius, presented a paper in Stockholm describing a patient with an expanding, circular, red rash following the bite of sheep tick that lasted several weeks.

• The rash was named “Erythema (red) Chronicum (lasts weeks) Migrans (expands) of Afzelius” or ECM.
Modern History of Lyme Disease

In November 1975 a mother from Old Lyme, Connecticut informed the SHD that 12 children from a small community of 5,000, 4 of whom lived on the same road, had a rare disease diagnosed as juvenile rheumatoid arthritis (JRA).

During the same month another mother from the same community reported at the Yale Rheumatology Clinic that she, her husband, 2 children and several neighbors all had arthritis.

Polly Murray who first reported what would become to be known as Lyme disease. Author of “The Widening Circle: A Lyme disease Pioneer Tells Her Story”

Dr. Allen Steere, who at the time was a Rheumatology Fellow at Yale University, was sent to investigate along with Dr. David Snydman of the Connecticut SHD
LYME ARTHRITIS
AN EPIDEMIC OF OLIGOARTICULAR ARTHRITIS IN CHILDREN AND ADULTS IN THREE CONNECTICUT COMMUNITIES
ALLEN C. STEELE, STEPHEN E. MALAWISTA, DAVID R. SNYDMAN, ROBERT E. SHOPE, WARREN A. ANDIMAN, MARTIN B. ROSE, and FRANCIS M. STEELE

Arthritis and Rheumatism 1977;20:7

Lyme Arthritis

• 51 residents (total population 5,400) had arthritis
  – Sudden onset
  – Large weight bearing joints (knee > ankle)
  – Lasted several weeks and resolved spontaneously
  – Many (70%) had recurrences
  – Often associated with fever, fatigue, headache, muscle aches (Flu-like symptoms)

Lyme Arthritis

• Other important observations:
  – A significant number recalled a red, expanding rash several weeks before the onset of arthritis
  – One person recalled a tick bite at the site of the rash
  – Most affected individuals lived on heavily wooded lots or on farms
  – Most cases of arthritis occurred from June to September
• Extensive studies on blood and joint fluid and could find no causative agent
Conclusions

• Clustering of cases suggested an infectious etiology —> unknown at the time
• Clustering of cases in wooded areas and peak occurrence in the summer months led “the authors to believe that the epidemiology fits best with an illness transmitted by an arthropod vector”
• Noted the similarity of the rash to ECM of Afzelius that was transmitted by Ixodes ricinus

Willie Burgdorfer, Ph.D.
R M Lab in Hamilton, MT

Jorge Benach, Ph.D.
SUNY at Stoneybrook

Alan Barbour, M.D.

Discovery of the Cause of Lyme Disease

• Scientific break through
• Serendipity
• An accident
• The result of 35 years of research into the complex relationship of ticks, the bacteria they harbor and their interaction with humans

Willie Burgdorfer’s Discovery

• 1946 accepted as grad student at U. of Basel
  – Mentor, Rudolph Geigy, was interested in blood-sucking ticks
  – Burgdorfer’s project was to study a borrelia species that caused disease in sheep and was transmitted by ticks
  – “For the next 3 years, I dissected thousands of ticks” and studied the replication of bacteria in the tick
  – Organisms replicate in the mid gut and disseminate—by cutting off the legs and collecting fluid (endolymph) can tell what organisms are in the tick
**Willie Burgdorfer’s Discovery**

- In 1949 he goes to a meeting in Cincinnati, Ohio
- Hears a paper by Hellerström on ECM of Afzelius
  - Claim is that it responds to antibiotics
  - Postulated, with little evidence, that it was transmitted Ixodes ricinus and caused by a spirochete i.e. a borrelia species
  - Considered heresy because spirochetes were carried by “soft” not “hard” ticks

- 1951 hired by Dr. Gordon Davis (“the world’s best known borreliologist”) at Rocky Mountain Laboratory in Hamilton, MT to continue his studies on borrelia
- Lack of funding for borrelia research —> turns to studying another tick borne disease RMSF caused by Rickettsia rickettsii transmitted by the dog tick, Dermacentor variabilis (“soft tick”)
- 1975 collaborates with Dr. Jorge Benach of the NYSHD because of an outbreak of RMSF on Long Island

**Willie Burgdorfer’s Discovery**

- 1977 Allen Steere calls to discuss the newly described Lyme arthritis and its association with Ixodes dammini
- In 1981 after examining 100’s-1,000s of dog ticks and not finding the cause of RMSF he asks Dr. Benach to send other ticks from Shelter Island—Ixodes dammini
- Sees an unusual parasite in the endolymph of 2 of 44 ticks
- Dissects the mid gut and he doesn’t see parasites, he sees.....
Willie Burgdorfer’s Discovery

- Recalls paper from 1949 on ECM of Afzelius and the postulation of a spirochetal cause; and discussion with Steere that Lyme arthritis is associated with Ixodes dammini.
- Dissects 124 more ticks and finds spirochetes in 60%
- Examines Ixodes ricinus and Ixodes pacificus ticks (Dr. Robert Lane from UC Berkeley) and finds spirochetes in them as well

Spirochetal Etiology of Lyme Disease

- Able to isolate spirochetes from humans with Lyme disease
- Able to isolate spirochetes from Ixodes dammini ticks
- Able to demonstrate an antibody response to the spirochetes in patients with Lyme disease
**Antibody Response to Infection**

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**Spirochetal Etiology of Lyme Disease**

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- Able to demonstrate an antibody response to the spirochetes in patients with Lyme disease
  - 94% of patients with late manifestations of Lyme disease had positive antibody titers

**Borrelia burgdorferi**

- Scientific break through
- Serendipity
- An accident
- The result of 35 years of research into the complex relationship of ticks, the bacteria they harbor and their interaction with humans

**Clinical Manifestations**

- Early localized infection (7-10 days after bite)
  - Erythema Migrans (70 – 80%)  
  - Fatigue, headache, fever, muscle aches and pains
- Early disseminated infection (weeks – months)
  - Skin
    - EM not at site of tick bite
  - Neurologic (15% of UNTREATED patients)
    - Meningitis, encephalitis, facial palsy, peripheral neuropathy (motor and sensory)
  - Heart (5% of UNTREATED patients)
    - Heart block
Clinical Manifestations

- Late Infection (months - years)
  - Arthritis (60% of UNTREATED patients)
    - Large weight bearing joints
  - Neurologic (5% of UNTREATED patients)
    - Peripheral neuropathy with pain, numbness and tingling
    - Mild encephalopathy with cognitive disturbances
    - Chronic encephalomyelitis with spasticity, ataxia (dizziness), severe cognitive impairment (Primarily seen in Europe with infection due to B. garinii. Very rare in the US)

Diagnosis

- Early Disease
  - Because of slow rise in antibody titers, diagnosis is made clinically in 1st two weeks
  - If repeat titers after 4 weeks almost all positive

Diagnosis of Late Manifestations

- CDC recommends 2-stage serologic testing
  - Screening ELISA—very sensitive but not specific
    - If negative—>no further testing
    - If positive—>confirmatory test
  - Confirmatory Western Blot

- Sensitivity of 2-tier testing in late Lyme disease is 100% and specificity is 99%
- “Therefore, current thinking is that all patients with objective neurologic, cardiac, or joint abnormalities associated with Lyme disease have serologic responses to B. burgdorferi”
Clues to Diagnosis

- EM occurs 3-30 days after bite—most commonly in 7-10 days
  - Early reactions that fade are due to the tick bite and are not EM
- Ticks must feed 24-36 hours to transmit organism
- Know prevalence in your area
  - East Coast 60-70% infected
  - West Coast < 5% infected
Prevention

- Light colored protective clothing with shirt tucked into pants and pants tucked into socks
- DEET
- Permethrin spray for clothes
- Tick checks with prompt removal

Prevention—Lyme Vaccine

- LYMERix licensed in 1998 (GlaxoSmithKline)
- 78% effective in preventing disease
- Removed from the market in 2002
  - A number of reasons, one of which was fear of lawsuits over possible adverse effects
Controversies in Lyme Disease

- IDSA (Infectious Disease Society of America)
- Alternate view of the disease
  - LLMDs—Lyme literate physicians
  - ILADS—International Lyme and Associated Disease Society in US
    - Own set of guidelines
    - Supported by powerful patient advocacy groups
  - European equivalents
    - German Borreliosis Society
    - Dutch Lyme Association

How Far Apart Are The Views?

- IDSA
  - Clinical Manifestations
    - Skin
    - Joints (arthritis)
    - Neurologic system
    - Heart
  - Diagnosis
    - 2-tier testing
    - 1993 study using "crude" (early) assay 94% had a positive test
    - 2008 article by Steere 99% with late disease had positive test
- ILADS/LLMDs
  - Clinical Manifestations
    - Fatigue
    - Low grade fever/hot flashes
    - Night sweats
    - Sore throat
    - Swollen glands
    - Stiff neck
    - Arthralgias/stiffness/less commonly arthritis
    - Myalgias
    - Chest pain/palpitations
    - Abdominal pain/nausea
    - Diarrhea
    - Sleep disturbance
    - Poor concentration and memory
    - Irritability and mood swings
    - Depression
    - Back pain
  - Diagnosis
    - Since there is no definitive test for Lyme disease, laboratory results should not be used to exclude an individual treatment
    - Lyme disease is a clinical diagnosis and tests should be used to support rather than supersede the physicians judgment
  - Therapy
    - Longest duration 28 days
    - May need to re-treat some with persistent arthritis
- ILADS/LLMDs
  - Therapy
    - Rather than an arbitrary 30-day treatment course, the patients clinical response should guide duration of therapy
    - Combination and sequential therapy that can last months
How Contentious Is It?

very

Antiscience and Ethical Concerns

- Antiscience groups and pseudoscientific practitioners
- Using unvalidated laboratory tests
- Various specialty laboratories in CA and KS that have been investigated and fined
- List current and former ILADS officers sanctioned by state medical boards or reprimanded by federal agencies

Counterpoint

- World Wide Lyme Rally & Protest May 10, 2013 Union Square, NYC—comments by Dr. Kenneth Liegner
<table>
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| • “Chronic Lyme disease does not exist”  
• There are at least four possibilities to explain why a person might hold this view:  
  – They can be “dumb as bags of rocks”  
  – They can be character-disordered, with exceeding rigid thinking, impenetrable, circular logic | • “Chronic Lyme disease does not exist”  
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  – They can be corrupt
  – They can be sociopaths
• One thing is for damn sure: they are truly lousy clinicians

How Contentious Is It?

The Clinical Assessment, Treatment, and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesiosis: Clinical Practice Guidelines by the Infectious Diseases Society of America

Gary F. Wormser1, Raymond J. Dattwyler,2 Eugene D. Hygema,3 John J. Halperin,4 Allan R. Steere,5 Mark D. Klempner,6 Peter J. Bannatyne,7 J. Robert Barbour,2 Joseph J. Dattwyler,2 Frances D. Delafield,8 Gerald Heppner,2 Linda Ilich,2 Donald Rich,9 Stephen Ecobichon,10 and Roger B. Nelson9

Clinical Infectious Diseases 2006;43:1089-1134
How Contentious Is It?

Shortly after the guidelines were published, then AG Blumenthal sued the IDSA saying the guidelines “severely constrict choices and legitimate diagnosis and treatment options of patients.” In addition, he accused the IDSA:
1. Several panelist had conflicts of interest
2. Panel refused to consider information about CLD
3. Refused to appoint panelists with divergent views on CLD

Law Suit Against IDSA

- Blumenthal ended suit in 2008
- Blumenthal & IDSA agreed to appoint a new committee vetted by both sides to review the data in the recommendations
- All day open public hearing to offer a forum for alternative views of the diagnosis and treatment of Lyme disease
  - 3 from Lyme advocacy groups
  - 4 ILADS/LLMDs

The Final Report--2010

- The Review Panel finds that the 2006 Lyme Guidelines were based on the highest-quality medical/scientific evidence available at the time and are supported by evidence that has been published in more recent years.
- The Review Panel did not find that the authors of the 2006 Lyme Guidelines had failed to consider or cite relevant data and references that would have altered the published recommendations.

Two Common Scenarios

- Scenario 1
  - Patient has documented Lyme disease and after therapy continues to have nonspecific symptoms
- Post-Lyme disease Syndrome
  - 129 patients total
    - 64 receive IV Ceftriaxone for 30 days followed by doxycycline 100 mg twice a day for 60 days
    - 65 receive IV dextrose solution for 30 days followed by oral pill that looks like doxycycline for 60 days
  - Evaluated at 30, 90 & 180 days
    - NO DIFFERENCE IN SYMPTOMS
Two Common Scenarios

- Scenario 2
  - Patient has nonspecific symptoms and no evidence of exposure to Borrelia burgdorferi i.e. antibody tests are negative
  
- This is where most of the “philosophical divide” occurs
  - They may have some underlying infection...BUT
    - I don’t think it is Lyme disease
    - I have seen no evidence that the symptoms respond to antibiotics

Some Observations

- Spirochetal diseases that affect humans
  - Relapsing fever (Borrelia recurrentis and other Borrelia spp)
  - Leptospirosis (Leptospira species)
  - Syphilis (Treponema pallidum)
  - Lyme disease (Borrelia species)

- Diagnosed with antibody studies &/or direct visualization
  - Relapsing fever—70% by visualization
  - Leptospirosis—55% by serology
  - Syphilis—95%-100% by serology

- Duration of therapy
  - Relapsing fever—single dose to 10 days
  - Leptospirosis—up to 7 days for severe disease
  - Syphilis—depends on stage of disease; neurosyphilis 10-14 days

Some Questions

- With all of the patients with “chronic Lyme disease” treated by LLMDs with long term antibiotics, why has there never been a randomized, double-blinded controlled study to see if antibiotics are any more effective than placebo?

Poly-ticks: Blue State versus Red State for Lyme disease-2004
Poly-ticks: Blue State versus Red State for Lyme disease-2004