Tick-Borne Disease Working Group
Tick-Borne Diseases Working Group

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Lyme Disease Overview

GOALS:
Improvements in prevention, detection and outcomes
Lyme Disease Overview

By illustrating several pivotal CDC promoted dogmatic guidelines contributing barriers to care:

- Diagnostics - “Two Tiered” system
- Concept of chronic Lyme disease
- Use of longer term antibiotics
Definitions

**Guideline**: information intended to advise people on how something should be done….

**Dogma**: a fixed belief or set of beliefs that people are expected to accept without any doubts

The “Two Tiered” System

Present DOGMA-tending to restrict diagnosis

“highly sensitive”

The “Two Tiered” System

Alternative interpretation of the literature

on average ~50% sensitive

The “Two Tiered” System

A disservice to patients when they are told with absolute certainty that Lyme disease “has been ruled out with a negative test”

Virginia Governor’s Task Force on Lyme

“there is no test that can absolutely rule out Lyme disease”

Commonwealth of Virginia The Governor’s Task Force on Lyme Disease
FINAL REPORT June 30, 2011
Chronic Lyme Disease

For purposes of this discussion:

A multi-system illness that is the result of an ongoing infection by any of several pathogenic members of the *Borrelia burgdorferi* sensu lato (*Bbsl*) complex
Chronic Lyme Disease

Present DOGMA > contributing to restriction of care:

“There is no convincing biologic evidence for the existence of symptomatic chronic *B. burgdorferi* infection among patients after receipt of recommended treatment regimens for Lyme disease.”

In essence, chronic Lyme disease does NOT exist

Chronic Lyme Disease

Alternative interpretation of the literature

Very MUCH exists and likely two forms:

• Post treatment
• Late, undiagnosed
Chronic Lyme Disease
Post Treatment
(after IDSA recommended protocols)

Evidence of Persistence [1-3]

Chronic Lyme Disease
Post Treatment

Short-term antibiotics fail in 25%-71% of patients with late stage disease [1-7]

Documented chronic and late manifestations of untreated, active infection [1-7]

Chronic Lyme Disease
Late, Undiagnosed

Contributing factors to increased incidence and delays in diagnosis

• Expanding tick exposure risk
• Contributing to increased incidence of Lyme disease [1]

Chronic Lyme Disease
Late, Undiagnosed
Delays in diagnosis-Unrecognized exposure

• Small vectors>tick bites frequently not noticed [1]
• Hallmark EM rash, frequently absent or misidentified [2,3]

Chronic Lyme Disease
Late, Undiagnosed

Delays in diagnosis-Clinical Presentation

• Often common clinical features: e.g., acute “flu like” illness, fatigue, joint pain, headaches, etc. [1]

• The “new ‘great imitator’” [2] “…confused with conditions such as multiple sclerosis, brain tumor, and psychiatric derangements.”

Chronic Lyme Disease
Late, Undiagnosed
Delays in diagnosis-Co-infections

• “…evidence for increased severity and duration of illness.” [1] Confounding clinical features and likely contributing to management challenges

Chronic Lyme Disease
Late, Undiagnosed

Delays in diagnosis-Diagnostics

- Poor sensitivity of diagnostic “two tiered” system [1,2]
- In the setting of influential guidelines [3] supported by the CDC, actually promoting a contradictory high sensitivity of this paradigm

Chronic Lyme Disease
Late, Undiagnosed

Contributing factors to delays in diagnosis

CDC recommendations decreasing likelihood for diagnosis

www.cdc.gov:

“Many doctors may not consider tick-borne diseases in diagnosing your illness unless you report being bitten by a tick”

But <50% of Lyme disease patients remember that exposure [1]

Longer Term Treatment with Antibiotics

Present DOGMA > tendency to restrict care

“There is no benefit of long term antibiotics in Lyme disease”

Longer Term Treatment with Antibiotics
Alternative interpretation of the literature

NIH sponsored trials

In sub-cohort analysis, two of the four trials provided evidence for the benefit of prolonged antibiotic treatment in chronic Lyme disease. [1,2]

Longer Term Treatment with Antibiotics

Alternative interpretation of the literature

NIH sponsored trials

The remaining two NIH trials had serious design flaws [1, 2]


1/24/2018 Samuel Shor, MD, FACP
Longer Term Treatment with Antibiotics

Alternative interpretation of the literature

Four trials that support the benefits of longer term treatment

CONCLUSIONS

• There is no place for dogma, particularly in a field for which there remain so many questions

• NEED for this working group to maintain an open, balanced interpretation of the literature

• This can then drive more appropriate education to clinicians, the public and governmental agencies

• Goals to improve prevention, detection and outcomes
Tick-Borne Disease Working Group
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Elizabeth Maloney, MD
Partnership for Tick-borne Diseases Education
December 12, 2017
Focus: Knowledge Gaps

- Prevention
- Pathogenesis
- Diagnosis
- Treatment

Lyme disease

- Multiply-infected individuals
Prevention

• Reducing exposure
  • Possible to reduce tick populations size/range expansion?

• Personal prevention practices
  • Motivators and barriers?
  • Comparative effectiveness of various practices

• Post-exposure prophylaxis
  • Single dose doxy$^{1,2}$ topical azithromycin$^{3}$ not highly efficacious
  • Multi-day antibiotic regimens?$^{4,7}$ Herbal agents?

Pathogenesis

- **Species and strain variations**
  - Tissue tropism\(^1\)
  - Disease presentation\(^2\)
  - Disease severity\(^3\)
  - Antibiotic susceptibility\(^4,5\)
    - Conflicting in vitro evidence

- **Host-pathogen interactions**
  - Why do some not become ill?
  - Cause for wide spectrum of manifestations?
    - Example: Why isn’t EM uniformly present?
      - Absence implications?
  - What allows for disease latency?
  - What triggers reactivation?

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\(^5\) Hunfeld KP. Antimicrob Agents Chemother. 2004
Pathogenesis

- Host-pathogen interactions
  - Are morphologic variants/persisters clinically relevant?\(^1\) \(^4\)
  - Why does the antibody response vary by presentation?\(^5\),\(^6\)
  - Is the immune response in sustained illness inherently different?\(^7\)
    - Strategic shift from eradication to containment?
  - What are the causes of post-treatment persistent manifestations?\(^8\),\(^9\)
    - How might *B. burgdorferi* survival mechanisms be thwarted?
    - Do inflammatory aspects of immune response continue after bacterial eradication?

\(^8\)Cameron D. Expert Rev Anti Infect Ther 2014. \(^9\)Chandra A. Brain Behav Immun 2010.
Diagnosis

• Need direct tests of infection
  • Immune response is unpredictable
  • Serology is unreliable\textsuperscript{1, 4}

• Demonstrated clinical (not bench) validity

Treatment

• Absence of high-quality trial data\textsuperscript{1,2}
  • Past studies inadequate – too small, design flaws and/or poorly analyzed

• May need to look beyond RCT designs

• Clinical trials may be futile when pathogenesis not understood

\textsuperscript{1} Cameron D. Expert Rev Anti Infect Ther 2014.
\textsuperscript{2} Hayes E. Clinical Evidence 2004.
Treatment Effectiveness, a Caution

• Treatment responses are heterogeneous; trials report averages

“misapplying averages can cause harm, by either giving patients treatments which do not help or denying patients treatments that would help them.”

Kravitz RL Milbank Q. 2004
Multiply-infected Individuals

• No treatment trials

• Pathogen-Pathogen synergy?
  • Increased disease severity\(^1\)
  • Decreased antibiotic effectiveness\(^2\)
    • Example: Zeidner study of doxycycline prophylaxis for preventing Lyme
      Effectiveness for B. burgdorferi exposure alone – 47%
      Effectiveness for B. burgdorferi when
      Simultaneous B.b and A. phagocytophilum – 20%

\(^1\)Krause PJ. JAMA 1996
\(^2\)Zeidner N. J Med Microbio 2008
Problematic Federal Activities Related to TBDs

• Prevention Campaigns are limited
• CDC/NIH
  • Perceived biases in Website content, publications, physician education
    • Reflects a particular worldview, not the entire body of evidence
  • Some Publications distort evidence
    • Example: xenodiagnostic paper
      Changed primary endpoint from that reported on clinicaltrials.gov
      Disavowed positive finding of persistent *B. burgdorferi* DNA.

Greatest Impact on the Greatest Number

In the here and now:

1. Awareness/Prevention Campaigns
   A. Leveraging what works
   B. Messaging that motivates

2. Provide meaningful physician education
   A. Enough available evidence for changing current practices
      i. Tick bites; risk stratification for treatment of early Lyme

3. Clean-up websites
   A. Evidence-based information
   B. Neutral analysis/presentation of literature
Greatest Impact on the Greatest Number

Future activities

1. Focus on understanding pathogenesis/immune response
2. Development of reliable direct tests for *B. burgdorferi*
3. Development of safe, effective, durable vaccine
4. Sponsor trials reflecting community circumstances and patient concerns
   A. All patient types, including multiply infected patients
   B. Patient-centered outcome definitions
   C. Community available resources
References

• Maloney EL. The management of Ixodes scapularis bites in the upper Midwest. WMJ. 2011 Apr;110(2):78-85.


References


References


• Dressler F, Whalen JA; Reinhardt BN; Steere AC. Western blotting in the serodiagnosis of Lyme disease. J Infect Dis 1993; 167(2): 392 -400.


• Ang CW, Notermans DW, Hommes M, Simoons-Smit AM, Herremans T. Large differences between test strategies for the detection of anti-Borrelia antibodies are revealed by comparing eight ELISAs and five immunoblots. Eur J Clin Microbiol Infect Dis 2011; 30(8):1027-32.


References

Strengthening the Prevention, Diagnosis and Treatment of Lyme Disease

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December 12, 2017
Evidence-based recommendations regarding tick-borne infections

- Strengthen surveillance
- Improve prevention
- Advance diagnostics
- Ensure all patients receive effective & safe treatment
- Understand mechanisms of persistent symptoms following therapy for Lyme disease
  - To inform useful therapeutic approaches
**Recommend:** funding increase for CDC Division of Vector-Borne Diseases supported surveillance

• Track Lyme and other tick-borne diseases
  – Especially emerging border regions

• Impact on different populations

• Evaluate interventions to prevent spread of Lyme disease and other tick-borne diseases, also

CDC, 2016 data
CDC studies with interventions to reduce tick populations failed to change the incidence of tick-borne diseases.

**Recommendation:**
Develop new measures for preventing tick-borne diseases
   Backed by robust studies to judge effectiveness.
Lyme Disease Vaccine: Learning from Past Challenges

• LYMERix: FDA approval (1998)
• Weak recommendation from ACIP/CDC
  – Lack of data in children < 15 yrs
  – Underreporting of Lyme disease
  – Cost concerns & exposure risks
• Unsubstantiated claims vaccine-induced arthritis
  – Market withdrawal by manufacturer (2002)


Hope on the horizon: At least five groups of academic or industry researchers working on Lyme vaccines
Lyme Disease Vaccine: Ideal Characteristics

- Protect against multiple *Borrelia* species and genotypes in US and Europe
- Provide multi-year protection, require as few doses/boosters as possible
- At least 80% efficacy
- No serious adverse reactions

Such a vaccine should be made standard for active children and active adults in states with endemic Lyme disease.

Source: Plotkin S. Need for a New Lyme Disease Vaccine. NEJM September 8, 2016
Lyme Disease Vaccine: Economics

- Vaccine development costly → long-term cost savings/public health improvements
- No likely standard vaccine recommendation for all 50 states
- Education regarding efficacy, safety and target populations

**Recommendation:** Review vaccine candidates, barriers to Lyme vaccine R&D. Consider ways to spur incentives for Lyme vaccine R&D.
Current State of Lyme Disease Diagnostics

• FDA-approved serologic tests remain only well-validated diagnostic method, if erythema migrans absent.
  – Existing molecular and culture-based assays of limited utility.
• The human immune response typically requires weeks for antibody generation against *Borrelia burgdorferi* bacteria.
  – Early Lyme disease is often seronegative.
  – Inherent limitation of antibody-based testing
  – Serology performs well as immune response builds
Progress in Lyme Disease Diagnostics

NIH and CDC Serum Reference Repository for researchers

• 2011: well-characterized Lyme disease patient histories and related serum samples
  – Allows comparison of newly developed tests compared to existing diagnostics

CDC and others developing next generation direct diagnostic tests and biomarkers
Lyme Disease Diagnostics: Needs

• Diagnostics and reporting
  – Reduce misinterpretation
  – Lessen false negatives and false positives
• Improved ability to detect early Lyme disease
• Tests that correlate with microbial cure
• Education about using diagnostic Lyme disease tests
  – Especially in endemic and border-endemic (e.g., OH, MI, IN, NC) states
  – Appropriate use and limitations
  – Avoid over-testing, over-diagnosis and over-treatment.

New tests: long lead time, clinical validation = high costs, in often low margin business
  » Working group should consider potential incentives to spur Lyme disease diagnostics development.
Lyme Disease Treatments

Early Lyme disease: effective, longer duration with no benefit

- Doxycycline 10-day
- Amoxicillin 14-day
- Cefuroxime axetil 14-day

Sources:
Sanchez E et al. Diagnosis, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: A review. JAMA. 2016
Lyme Disease: Additional Antibiotic Treatment Does Not Help

Persisting symptoms beyond initial treatment for confirmed Lyme disease
Evidence of active infection not found

Additional antibiotics have not proven sufficiently or durably helpful compared to a placebo in multiple randomized placebo-controlled trials

Sources:
Neurology 60:1923-30, 2003
Lyme Disease: Dangers of Inappropriate Treatment (2017)

5 patients with complications of new, serious bacterial infections arising due to treatment for chronic Lyme disease: examples

Patient A: Intravenous treatment for chronic Lyme disease, Babesia and Bartonella in woman, late 30s, fatigue, joint pain. Death due to septic shock related to central venous catheter-associated bacteremia.

Patient B: Adolescent girl, muscle/joint pain, lethargy. Long term IV antibiotics through PICC line. Developed *Acinetobacter* infection, requiring ICU stay.
Lyme Disease Treatment: Research Needs

**Post-treatment Lyme disease Syndrome**

- Mechanistic understanding

- Effective therapies to eliminate or reduce
Tick-Borne Disease Working Group
Tick-borne Disease Challenges to Public Health

HHS Tick-borne Disease Working Group Meeting
Tuesday, December 12, 2017
Council of State and Territorial Epidemiologists

- Epidemiologists at state, territorial, local and tribal health departments
- Promotes effective use of epidemiologic data to guide public health practice and improve health
- Supports effective public health surveillance and epidemiologic practice through training, capacity development and peer consultation
Epidemiologists Linked to Several Essential Public Health Services, Primarily:

1. Monitor health status and burden to identify and solve community health problems
2. Diagnose and investigate health problems and health hazards in the community
3. Inform, educate, and empower people about health issues
Public Health Authority and Protection of Patient Confidentiality

- Public health has broad authority to collect data to prevent and control disease and protect public health; *(Whalen v. Roe (1977))*
- State and local health and Sanitary Codes authorize receipt and investigation of reportable disease data
  - Laboratory reporting and electronic laboratory reporting (ELR), case reporting, case and contact investigation and management, outbreaks and “unusual manifestations of disease”
- Health Insurance Portability and Accountability Act (HIPAA) permits protected health information (PHI) disclosure to public health without patient consent
- Confidentiality is rigorously protected by Public Health laws at all times; Information use is limited to the purpose for which it was collected *(308(d) of the Public Health Service Act)*
- Information that could result in the identification of an individual is not released
Tick-borne Disease Surveillance

• Lyme disease, anaplasmosis, babesiosis, Powassan virus disease, and other tick-borne diseases
• Helps to monitor both current and emerging disease trends over time and space
• Standardized case definition
  • Specific
    • A counted case is likely a real case
    • Not all cases counted due to clinical diagnosis only (no lab tests), non-reporting, variability in capacity at health departments
• Endemic states have massive burden, most useful in parts of the United States where diseases are emerging
• Risk factor data and development of specific prevention messages
• Platform for research
Data Driven Prevention Efforts

• Educate health care professionals about the changing distribution of disease and emerging tick-borne diseases
• Educate the public about the importance of tick bite prevention
What Is Needed

- Better diagnostics, especially for diseases where diagnosis is based on antibody detection rather than pathogen detection
- Improved access to laboratory testing for emerging diseases such as Powassan
- Support for development of public health infrastructure with less focus on disease-specific resources
- Electronic health records and real time disease reporting processes (e.g. electronic laboratory reporting and electronic case reporting) critical to sustainability
- Basic research into methods of effective vector control
- Assistance with outreach to achieve widespread behavioral changes around personal prevention
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