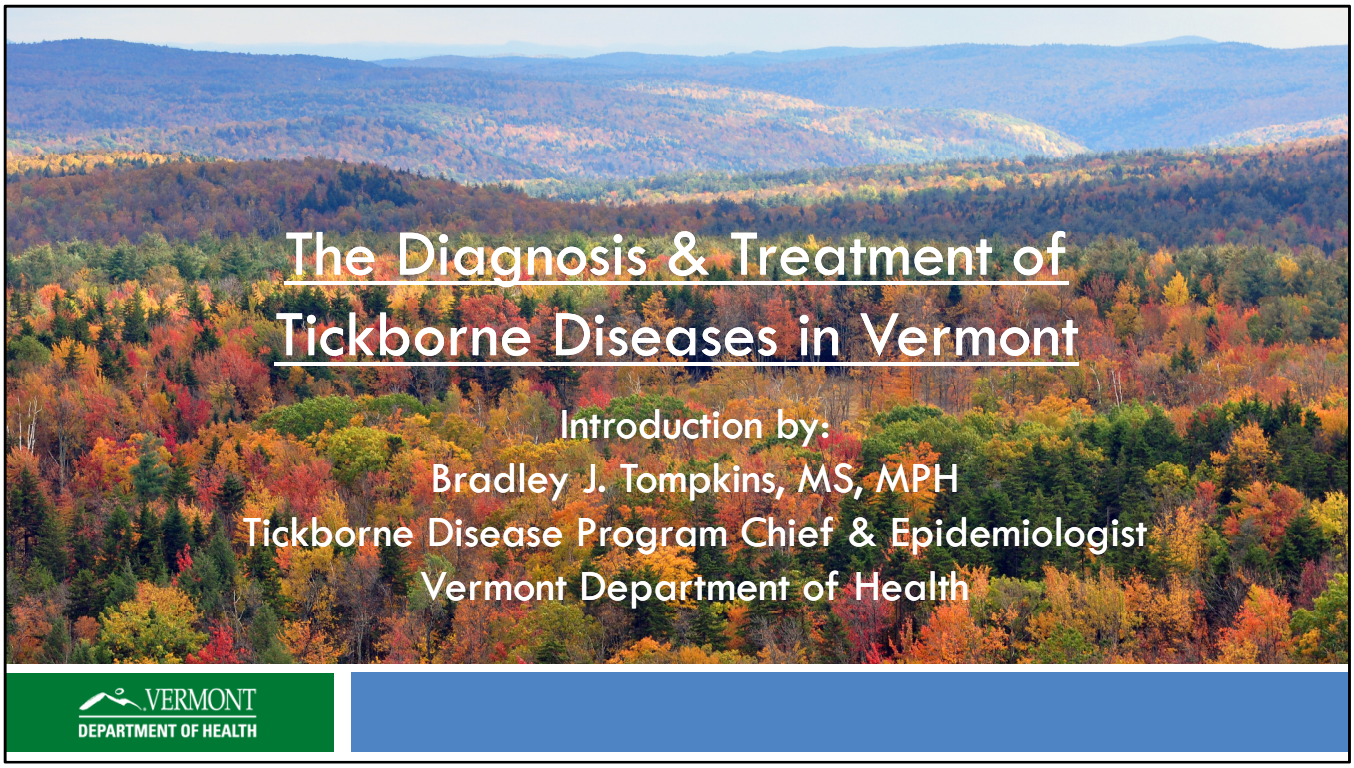

The Diagnosis & Treatment of Tickborne Diseases in Vermont

Introduction by:
Bradley J. Tompkins, MS, MPH
Tickborne Disease Program Chief & Epidemiologist
Vermont Department of Health

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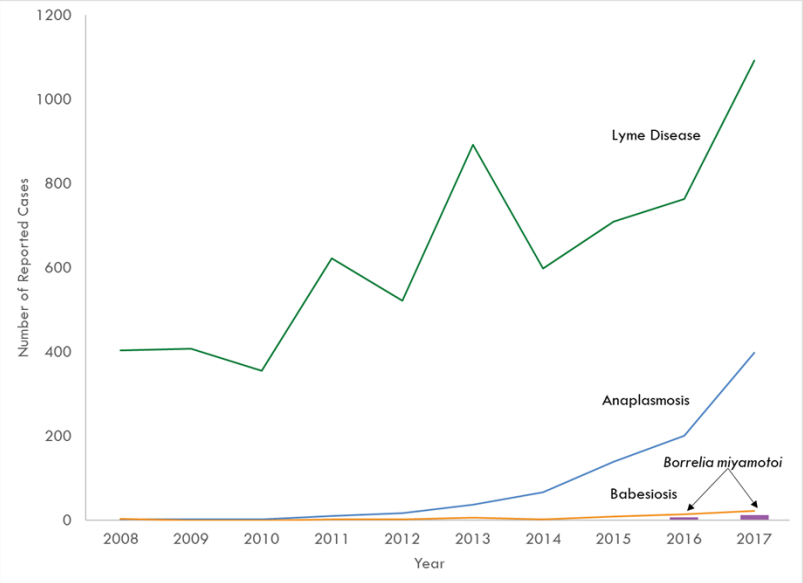
Tickborne Diseases Indigenous to Vermont

1. Lyme Disease
2. Anaplasmosis
3. Babesiosis
4. *Borrelia miyamotoi*
5. Powassan Virus Disease
   - Rare disease – last reported case in Vermont was in 1999
   - Underdiagnosed (?) – testing is only available through public health lab (CDC)
   - www.healthvermont.gov/disease-control/tickborne-diseases/powassan-virus

Tickborne Diseases Indigenous to Vermont (continued)



Blacklegged Tick (*Ixodes scapularis*)

Adult Female

Adult Male

Nymph

- Responsible for transmitting all reported tickborne diseases indigenous to Vermont
- Infection rate of ticks collected in Vermont:
  - *Anaplasma phagocytophilum*: 8%
  - *Babesia microti*: 2%
  - *Borrelia burgdorferi*: 51%
  - *Borrelia miyamotoi**: <1%

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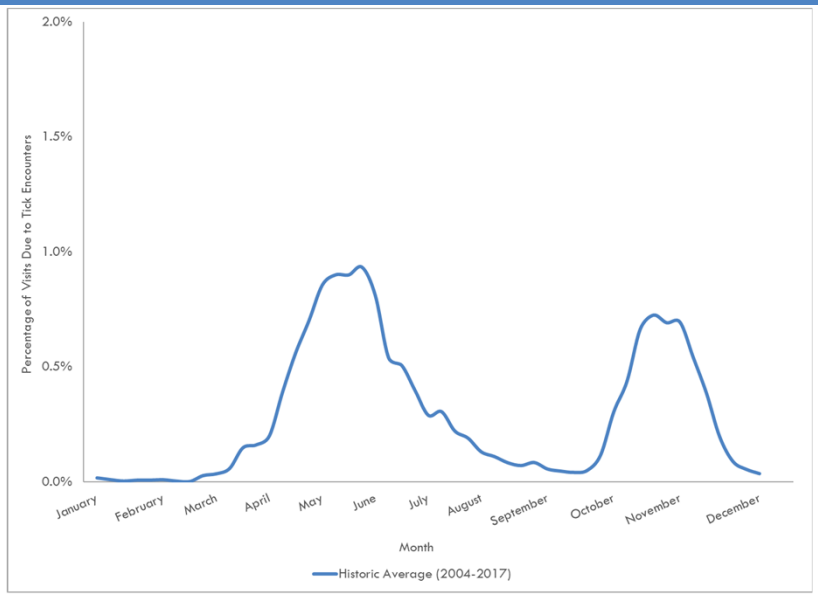
*small sample size

Blacklegged Tick (*Ixodes scapularis*) (continued)



Lyme Disease

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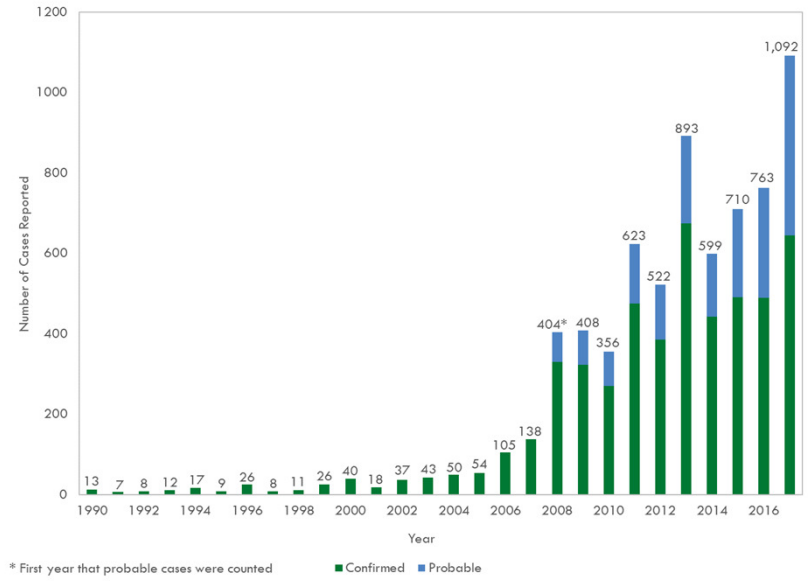
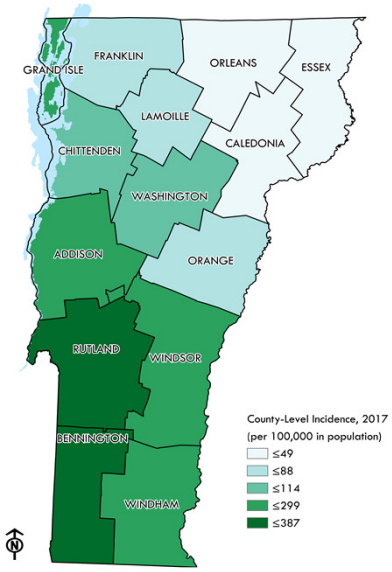
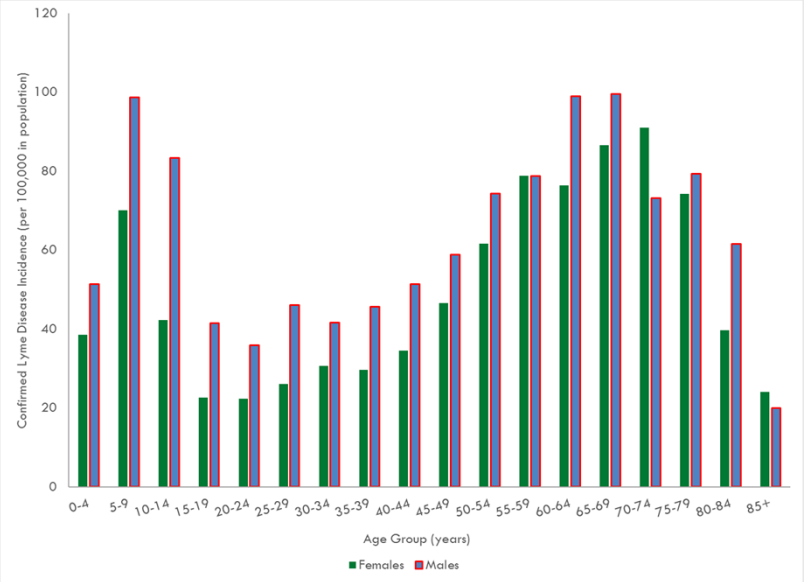
Changes in Lyme Disease Over Time and Geography



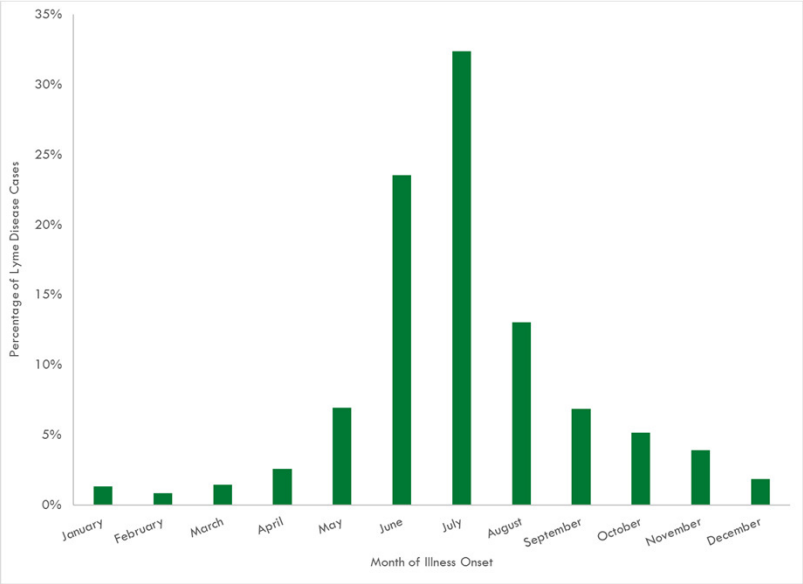


Demographics of Lyme Disease in Vermont



- Vermonters of all age groups are at risk for Lyme
- Higher risk groups:
  - Children between 5-14 years
  - Middle-aged & older adults
  - Males

Seasonality of Lyme Disease in Vermont



- Cases of Lyme disease occur throughout the year
- Over half all cases become sick in June & July

Diagnosis and Treatment Tickborne Diseases in Vermont
Part I:
Lyme Disease

Jean Dejace, MD

Infectious Disease Physician

The University of Vermont Medical Center

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Objectives

- Common clinical presentations
- Diagnosis and testing pitfalls
- Typical treatment regimens
- Outcomes
- Review some of the evidence behind current treatment guidelines
- Controversy

Primer: Laboratory Testing In Lyme Disease

- Testing is imperfect
  - Lyme is difficult to culture
    - insensitive
    - takes several weeks to grow
  - Diagnosis is based on clinical presentation and serologic testing
- Sensitivity of serology (CDC 2-tiered testing)
  - Erythema migrans : <50%
  - Early disseminated disease: ~80%
  - Late disease: >95%

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References:

Medscape 2016 CME pitfalls review

Aguero 2005

Two-Tier Testing

- First: Enzyme Immunoassay
  - tests for IgG and IgM
  - rapid, easily automated
  - easy to interpret: positive/negative/equivocal
  - not as specific
    - cross-reacting Ab in e.g. syphilis, leptospirosis, mono, autoimmune disease, periodontal disease
- *If* positive or equivocal EIA, *then* Western Blot
  - Highly specific

Two-Tier Testing

- Problems with the Western Blot
  - Costly
  - Subjective interpretation on the laboratory end
  - 10 IgG bands and 3 IgM bands are tested
- Results
  - 2 or more IgM bands = positive
  - 5 or more IgG bands = positive
- Typically sent to reference labs

Two-Tier Testing (continued)

ORIGINAL ARTICLE INFECTIOUS DISEASES

High frequency of false positive IgM immunoblots for *Borrelia burgdorferi* in Clinical Practice

V. Seriburi, N. Ndukwe, Z. Chang, M. E. Cox and G. P. Wormser
Division of Infectious Diseases, New York Medical College, Valhalla, NY, USA

Abstract

Although it is known that two-tier serologic testing for Lyme disease may be associated with false positive results on the IgM immunoblot, this problem has never been systematically studied in the clinical practice setting. In a retrospective investigation of patients referred to the private adult practice of an Infectious Diseases physician for possible for Lyme disease, 50 of 182 patients (27.5%, 95% CI: 21.1–34.6) were found to have a false positive IgM immunoblot. 78.0% of these patients had received unnecessary antibiotic therapy. False positive results were not restricted to any single commercial laboratory. Research on alternative testing strategies that eliminate the IgM immunoblot entirely is warranted.

Clin Microbiol Infect. Dec; 18: 1236-40 DOI: 10.1111/j.1469-0691.2011.03749.x

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Lyme Specialty Labs and Alternative Criteria

- As part of this investigation, blood from 40 healthy controls were sent to reference and specialty labs.
  - No history of prior diagnosis or treatment for Lyme
  - No history of Lyme-like symptoms
  - No history of another major medical disorder
  - Lack of residence or recent exposure to highly Lyme-endemic area
- 57.5% of healthy controls had a positive Lyme blot at one well-known specialty lab. None were positive by two-tier testing using CDC criteria.

Lyme Specialty Labs and Alternative Criteria (continued)

MAJOR ARTICLE

A Comparison of Lyme Disease Serologic Test Results From 4 Laboratories in Patients With Persistent Symptoms After Antibiotic Treatment

Brian A. Fallon,[1] Martina Pavlicova,[2] Samantha W. Coffino,[3] and Carl Brenner[4]

Departments of [1]Psychiatry, [2]Biostatistics, Mailman School of Public Health, [3]Neurology, Columbia University, and [4]Lamont-Doherty Earth Observatory of Columbia University, Palisades, New York

(See the Editorial Commentary by Dattwyler and Arnaboldi on pages 1711–3.)

Background. As the incidence of Lyme disease (LD) has increased, a number of "Lyme specialty laboratories" have emerged, claiming singular expertise in LD testing. We investigated the degree of interlaboratory variability of several LD serologic tests—whole cell sonicate (WCS) enzyme-linked immunosorbent assay (ELISA), immunoglobulin M (IgM) and immunoglobulin G (IgG) Western blots (WBs), and an ELISA based on the conserved sixth region of variable major protein–like sequence expressed (C6)—that were performed at 1 university laboratory, 1 commercial laboratory, and 2 laboratories that specialize in LD testing.

Methods. Serum samples from 37 patients with posttreatment Lyme syndrome, as well as 40 medically healthy controls without prior LD, were tested independently at the 4 laboratories.

Clin Infect Dis. 2014 Dec 15;59(12):1705-10. doi: 10.1093/cid/ciu703. Epub 2014 Sep 2.

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Laboratory Testing in Lyme Disease

- A good review on testing is available here:

Current Guidelines, Common Clinical Pitfalls, and Future Directions for Laboratory Diagnosis of Lyme Disease, United States

https://wwwnc.cdc.gov/eid/article/22/7/pdfs/15-1694.pdf

Diagnosis of Early Localized Lyme Disease

- Predominantly clinical based on erythema migrans
  - Present in ~75% of cases
  - Typically 1-2 weeks after tick exposure (3-30 day range)

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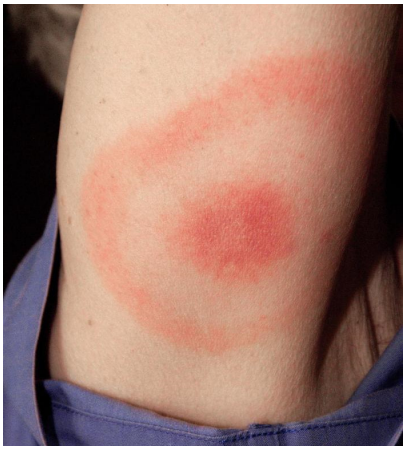
72% of reported cases MMWR 2008-2015

Erythema Migrans

"Classic" Lyme Disease Rash



CDC/James Gathany

- Recommended: https://www.cdc.gov/lyme/signs_symptoms/rashes.html

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Round or oval expanding erythematous skin lesion that develops at the site of tick bite

Should be >5cm

Sometimes no bullseye, central clearing or homogeneously erythematous. Can be more purpuric. Can have central vesicles or crust. Can be pruritic.

Common in axillae, groin/belt line, behind the knee

Diagnosis of Early Localized Lyme

- Systemic symptoms can occur in patients with single EM as well as in disseminated disease, resembling a viral syndrome without respiratory symptoms.
- 79 patients with EM (14 with multiple)
  - 68% had systemic symptoms
    - Fatigue – 54%
    - Arthralgia/Myalgia – 44%
    - Headache – 42%
    - Subjective fever/chills – 39% (documented in 16%)

The Clinical Spectrum of Early Lyme Borreliosis in Patients with Culture-confirmed Erythema Migrans

Robert B. Nadelman, MD, John Nowakowski, MD, Gilda Forseter, RN, Neil S. Goldberg, MD, Susan Bittker, MS, Denise Cooper, BS, Maria Aguero-Rosenfeld, MD, Gary P. Wormser, MD, *Valhalla, New York*

Am J Med. 1996 May;100(5):502-8

Diagnosis of Early Localized Lyme Disease

- In the presence of a typical EM rash, laboratory testing is not necessary and can confound the diagnosis
  - Serologic testing is insensitive in early localized disease
  - If serology sent in the presence of a typical EM rash, therapy should not be stopped if testing returns negative

Diagnosis of Early Localized Lyme Disease

- If there is diagnostic uncertainty…
  - Obtain baseline and follow-up serology 4 weeks later
  - Can treat patient empirically based on your clinical suspicion and their preference, or await repeat testing
  - Caveats
    - If the patient has known history of Lyme disease or previously positive serology, repeat testing is unlikely to be helpful. You have to decide on treatment without testing.
    - If you make a decision in your office to pursue the testing strategy without treatment, and the initial test returns positive, then don't wait 6 weeks to treat.

Clinical Features of Early Disseminated Lyme

- Weeks to months after infection
- Typical presentations
  - Skin
  - Cardiac
  - Neurologic

Early Disseminated Lyme: Skin

Multiple rashes, disseminated infection

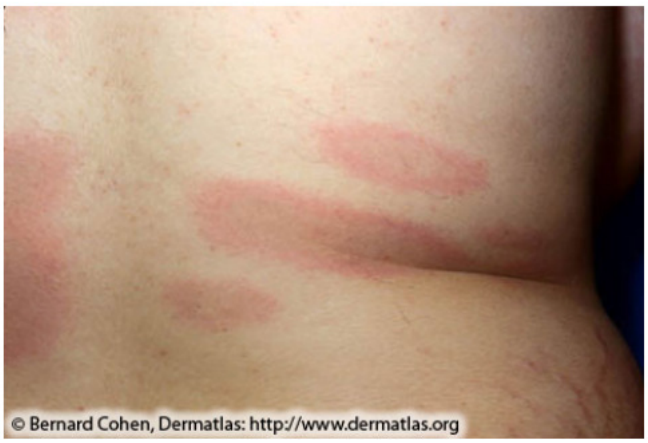

Photo Credit: Bernard Cohen

Description:

Early disseminated Lyme disease

[https://www.cdc.gov/lyme/signs_symptoms/rashes.html]

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Early Disseminated Lyme: Cardiac

- Uncommon (<2% of cases reported to CDC)
- Typically manifests as AV block within 2 months of infection
  - can be life-threatening if severe
- Can occur in isolation, or with EM/neurologic disease
- Diagnosis
  - History (endemic area, tick exposure)
  - Clinical features (i.e., recent or current EM rash)
  - EKG
  - Most have positive serology

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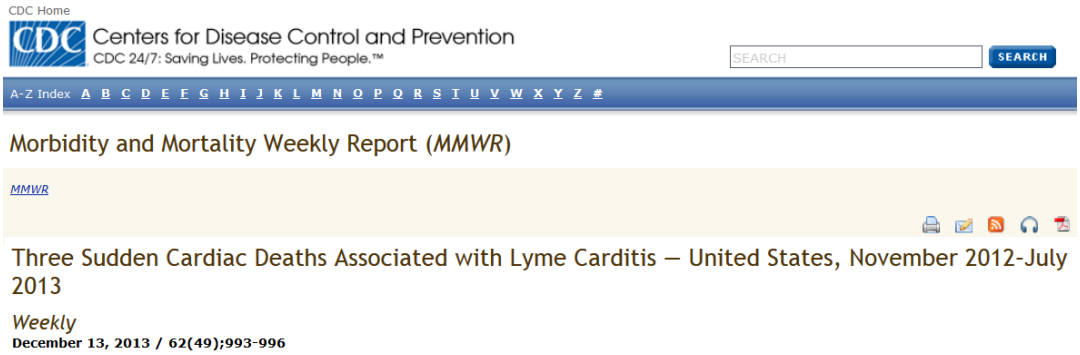
In Steere's original carditis case series published in 1980, 15 of 20 had EM

1.5% carditisi: MMWR 2008-2015 data from 275k cases
https://www.cdc.gov/mmwr/volumes/66/ss/pdfs/ss6622-H.pdf

Early Disseminated Lyme: Cardiac (continued)


CDC Home

Centers for Disease Control and Prevention

CDC 24/7: Saving Lives. Protecting People.™

SEARCH

SEARCH

A-Z Index A B C D E F G H I J K L M N O P Q R S T U V W X Y Z #

Morbidity and Mortality Weekly Report (*MMWR*)

MMWR

Three Sudden Cardiac Deaths Associated with Lyme Carditis — United States, November 2012-July 2013

Weekly

December 13, 2013 / 62(49);993-996

Early Disseminated Lyme: Neurologic

- About 1 in 8 reported cases
- Most common presentation is cranial neuropathy
  - Typically CN VII, can be bilateral
  - ~8% of reported Lyme cases have facial palsy
- Aseptic meningitis (often concurrently with above)
  - Less common, ~1% of reported Lyme cases
  - Less severe presentation than bacterial meningitis
    - Subacute headache, neck stiffness are typical
- Radiculopathy

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Incidence data: MMWR 2008-2015 data

Early Disseminated Lyme: Neurologic

- LP to evaluate meningitis symptoms
  - CSF will show moderate lymphocytic pleocytosis
- Most have positive serology (~80%)
- In some cases of diagnostic uncertainty (e.g. previously positive serology) can consider:
  - CSF antibody index (must draw concurrent serum)

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80%: Wormser 2013 Single Tier Testing w/ C6 Peptide compared w/ two-tier testing

Clinical Features of Late Lyme Disease

- Arthritis
  - Most commonly occurs months after infection
    - Can be weeks or years
    - Can present in colder months, when other forms less common
  - Eventually develops in ~60% of untreated patients
  - Currently in ~25% of reported cases
    - More patients diagnosed and treated in early stages
    - Remains most common manifestation of disseminated disease

Clinical Features of Late Lyme Disease

- Arthritis
  - Objective evidence of joint inflammation
    - Warmth, swelling, redness
    - Contrast: diffuse arthralgias can occur in early disease
  - Mono or oligoarticular
    - In either case, typically involves the knee
    - Other large joints or TMJ can be involved
  - Pain relatively minimal and fever rare
    - Contrast with septic arthritis
  - Intermittent
    - Episodes of arthritis last weeks to months if untreated

Clinical Features of Late Lyme Disease

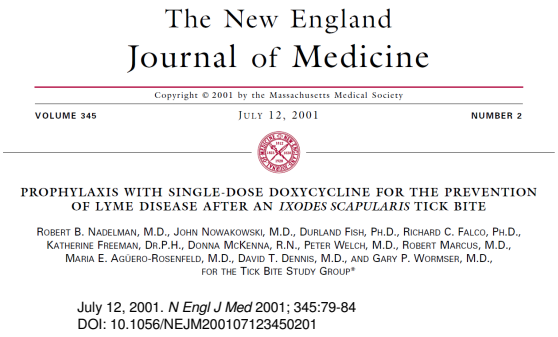
- Arthritis
  - Diagnosis
    - Objective evidence of joint inflammation + serology
    - Synovial fluid analysis: cell count, crystals, culture
      - Establish presence of inflammatory arthritis (i.e. elevated WBC)
      - Rule out other etiologies (septic arthritis, crystal arthropathy)
      - Lyme: typically mild/moderate elevation in WBC <25,000

Treatment

- Overview
  - PO doxycycline is the treatment of choice in most cases
    - IV ceftriaxone should be used for a limited number of indications
  - Short courses of therapy are the standard of care

Treatment of Tick Bites

- 482 subjects who had removed an *Ixodes* tick acquired in Westchester County, NY in the past 72 hours
- They were randomized into 2 groups
  - 235 received a single 200mg dose of doxycycline
  - 247 received placebo
- Primary outcome
  - Development of EM rash



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Largest study on this topic by far. Other smaller ones are in the Discussion section. The others found no benefit.

Treatment of Tick Bites

- Results
  - Placebo group: 8 of 247 developed EM (3.2%)
  - Doxycycline group: 1 of 235 developed EM (0.4%)

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89% follow up at 6 weeks

Best evidence we've got, but imperfect. Large confidence interval due to small # of EM.

Hard to justify giving longer courses based on this (ie >240 unnecessary 3 week courses since relatively few people seem to develop EM/Lyme after a bite)

Treatment of Tick Bites

- A single dose of 200mg doxycycline is offered *if*
  - *Ixodes* tick attached for >36h
  - Prophylaxis can be started within 72h of removal

Treatment of Early Localized Lyme

- Treatment is PO
- 1 of 3 antibiotic regimens is recommended
  - Doxycycline 100mg BID
    - Note: doxycycline also treats anaplasma (others do not)
  - Amoxicillin 500mg TID
  - Cefuroxime 500mg BID
- Duration
  - 14-21 days (10 days is effective with doxycycline)

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Treatment of Early Localized Lyme

- Evidence for good clinical outcomes
- Notable studies
- Luger et al., 1995: 232 subjects, doxy vs. cefuroxime
  - Success or improvement in
    - 95% of doxycycline treated patients
    - 90% of cefuroxime treated patients

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 1995, p. 661–667 Vol. 39, No. 3
0066-4804/95/$04.00+0

Comparison of Cefuroxime Axetil and Doxycycline in Treatment of Patients with Early Lyme Disease Associated with Erythema Migrans

STEVEN W. LUGER,[1] PHILIP PAPARONE,[2] GARY P. WORMSER,[3] ROBERT B. NADELMAN,[3] EDGAR GRUNWALDT,[4] GEMA GOMEZ,[5] MICHAEL WISNIEWSKI,[5] AND JEFFREY J. COLLINS[5]*

Old Lyme Family Practice, Old Lyme, Connecticut[1]; Lyme Disease Center for South Jersey, Absecon, New Jersey[2]; Division of Infectious Diseases, Department of Medicine, New York Medical College, Westchester County Medical Center, Valhalla, New York[3]; Shelter Island, New York[4]; and Glaxo Inc., Research Triangle Park, North Carolina[5]

Treatment of Early Localized Lyme

- Evidence for good clinical outcomes
- Notable studies
  - Wormser et al., 2003: 180 subjects
    - 60 received IV CTX x1 + 10 days PO doxycycline
    - 61 received 10 days PO doxycycline
    - 59 received 20 days PO doxycycline
  - No significant difference in outcomes at 20 days, 3 months, 12 months or 30 months

Annals of Internal Medicine | ARTICLE

Duration of Antibiotic Therapy for Early Lyme Disease

A Randomized, Double-Blind, Placebo-Controlled Trial

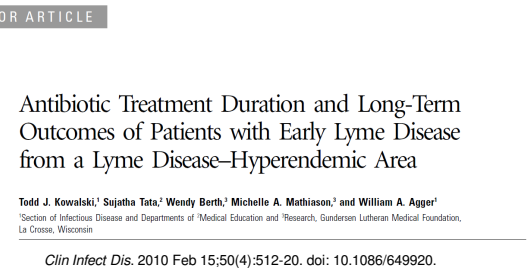
Gary P. Wormser, MD; Roshan Ramanathan, MD, MPH; John Nowakowski, MD; Donna McKenna, RN, ANP; Diane Holmgren, RN; Paul Visintainer, PhD; Rhea Dornbush, PhD; Brij Singh, MD; and Robert B. Nadelman, MD

Ann Intern Med. 2003 May 6;138(9):697-704

Similar efficacy, notably even 10 days doxy

Treatment of Early Localized Lyme

- Evidence for good clinical outcomes
- Notable studies
  - Kowalski et al., 2001
  - Retrospective study of 607 patients with early Lyme
  - 93% treated with doxycycline
  - Outcomes: "treatment failure-free" at 2 years
    - </= 10 days of antibiotic: 99%
    - 11-15 days of antibiotic: 98.9%
    - >/= 16 days of antibiotic 99.2 %



MAJOR ARTICLE

Antibiotic Treatment Duration and Long-Term Outcomes of Patients with Early Lyme Disease from a Lyme Disease–Hyperendemic Area

Todd J. Kowalski,[1] Sujatha Tata,[2] Wendy Berth,[3] Michelle A. Mathiason,[3] and William A. Agger[1]

[1]Section of Infectious Disease and Departments of [2]Medical Education and [3]Research, Gundersen Lutheran Medical Foundation, La Crosse, Wisconsin

Clin Infect Dis. 2010 Feb 15;50(4):512-20. doi: 10.1086/649920.

Treatment of Early Localized Lyme

- 100 patients with erythema migrans recruited 1991-2000
  - Treated on presentation
  - Assessed 2011-2013
  - Outcome: Health Related Quality of Life by SF-36v2
- Results:
  - Mean follow-up 15.4 years
  - Scores similar to general U.S. population

BRIEF REPORT

Long-term Assessment of Health-Related Quality of Life in Patients With Culture-Confirmed Early Lyme Disease

Gary P. Wormser,[1] Erica Weitzner,[1] Donna McKenna,[1] Robert B. Nadelman,[1] Carol Scavarda,[1] Irida Molla,[1] Rhea Dornbush,[2] Paul Visintainer,[3] and John Nowakowski[1]

[1]Division of Infectious Diseases, and [2]Department of Psychiatry, New York Medical College, Valhalla; and [3]Baystate Medical Center, Springfield, Massachusetts

Paper on improvement/same as general population

Treatment of Early Disseminated Lyme

- Disseminated erythema migrans
  - Treatment is same as localized EM
- Cardiac disease
  - Hospitalize with cardiac monitoring if
    - Symptomatic (e.g. syncope)
    - Advanced heart block
  - May need to consider temporary pacemaker
  - Treat hospitalized patients with IV ceftriaxone initially
  - Duration: 14-21 days (can complete with PO therapy)

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Hospitalize: symptomatic (dyspnea, syncope, chest pain), 2nd/3rd AV block or PR >300ms

IV CTX is expert opinion

Treatment of Early Disseminated Lyme

- Neurologic disease
  - Isolated cranial nerve palsy without signs of meningitis (e.g. headache, nuchal rigidity) is often treated with the typical PO antibiotic regimens.
    - Palsy can take several weeks to resolve
  - Meningitis and radiculopathy are preferably treated with IV ceftriaxone 2g daily for up to 28 days

Treatment of Late Lyme Disease

- Arthritis
  - PO therapy is preferred (decreased cost and side-effects)
    - Doxycycline 100mg BID for 28 days
    - Amoxicillin 500mg TID for 28 days
    - Cefuroxime 500mg BID for 28 days
  - Symptoms often slow to resolve
  - If persistent symptoms weeks to months after initial Rx
    - Either:
      - Repeat PO therapy x28 days (typically if incomplete response)
      - IV ceftriaxone x28 days (typically if little to no response to PO)

Treatment of Late Lyme Disease

- Arthritis
  - If symptoms persist after two courses of antibiotics
    - Trial NSAIDs or hydroxychloroquine
    - Consider methotrexate if severe
  - If symptoms still persist for several months
    - Consider arthroscopic synovectomy

Review for reference

Treatment of Late Lyme Disease (continued)

Diagnosis and Treatment of Lyme Arthritis

Sheila L. Arvikar, MD, Allen C. Steere, MD*

KEYWORDS

- Lyme disease • *Borrelia burgdorferi* • Lyme arthritis • Antibiotic-refractory arthritis
- Inflammatory arthritis

KEY POINTS

- Lyme arthritis is a late disease manifestation, usually beginning months after the tick bite. Patients may not report an antecedent tick bite or erythema migrans.
- Patients have intermittent or persistent attacks of joint swelling and pain, primarily in 1 or a few large joints, especially the knee, without prominent systemic manifestations.
- The diagnosis is supported by 2-tier serologic testing for *Borrelia burgdorferi* by enzyme-linked immunosorbent assay and immunoglobulin G Western blotting.
- Initial treatment is a 30-day course of oral doxycycline or amoxicillin. For patients with an insufficient response to oral treatment, intravenous therapy with ceftriaxone is recommended.
- A minority of patients may have persistent synovitis for months or several years after oral and intravenous antibiotic therapy, which is treated with antiinflammatory agents, disease-modifying antirheumatic drugs, or synovectomy.

Infect Dis Clin North Am. 2015 Jun;29(2):269-80. doi: 10.1016/j.idc.2015.02.004

Review: Possible Indications for IV Therapy

- There are three:
  - Neurologic disease
  - Advanced atrioventricular block
  - Refractory arthritis
- PO therapy is otherwise the standard of care.

Review: Possible Indications for IV Therapy (continued)

Long-term Follow-up of Patients with Culture-Confirmed Lyme Disease

John Nowakowski, MD, Robert B. Nadelman, MD, Rebecca Sell, Donna McKenna, L. Frank Cavaliere, MD, Diane Holmgren, Adriana Gaidici, MD, Gary P. Wormser, MD

PURPOSE: To determine the long-term outcome of patients with culture-confirmed Lyme disease.

METHODS: We analyzed data collected prospectively on adult patients from a highly endemic area in New York State who were diagnosed with early Lyme disease between 1991 and 1994. Patients with culture-confirmed erythema migrans were evaluated at baseline, 7 to 10 days, 21 to 28 days, 3 months, 6 months, 1 year, and annually thereafter. All patients were treated with antibiotics at the time of diagnosis.

RESULTS: We evaluated 96 cases on 709 separate occasions (median, eight evaluations per case). The erythema migrans rash resolved within 3 weeks in all of the 94 evaluable cases, none of whom developed an objective extracutaneous manifestation of Lyme disease. Of the 81 cases who were followed for ≥1 year, all but 8 (10%) were asymptomatic at their last visit, a mean (± SD) of 5.6 ± 2.6 years into follow-up, and only 3 (4%) were symptomatic at every follow-up visit. Intercurrent tick bites were reported by 45 cases (47%), and 14 (15%) developed a second episode of erythema migrans. Four other cases who were asymptomatic seroconverted between years 2 and 5.

CONCLUSION: The long-term outcome of patients with erythema migrans after antibiotic therapy was excellent, but patients from a highly endemic area in New York State remained at high risk of re-exposure to ticks and reinfection. Subjective symptoms during follow-up evaluations tended to be mild to moderate, intermittent, and associated with more symptomatic illness at the time of initial diagnosis. **Am J Med. 2003;115: 91–96.**

Vermont Department of Health

Outcomes

- 96 patients with erythema migrans
  - All treated with short course antibiotics on presentation
  - All evaluable patients (94/96) resolved EM at 3 weeks
  - No objective findings of late Lyme disease in any patient
  - Asymptomatic
    - >50% at 10 days
    - 80% at 28 days
    - 90% at 6 months

Chronic, Non-Specific Symptoms

- Fatigue
  - Present in up to 30% of the general population
- Muscle and joint aches without objective clinical or laboratory evidence of inflammation
- Difficulty concentrating, mental "slowness"
- Post-Treatment Lyme Disease Syndrome
  - often referred to as "chronic Lyme"

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Chronic fatigue 25%

Chronic, Non-Specific Symptoms

- Is there a basis for Lyme as a chronic infection?
  - DNA (PCR) has been found in tissue after antibiotic treatment in animals.
  - Overwhelmingly, no borrelia has grown from culture after treatment in these animal experiments (i.e. active division suggesting a viable pathogen).
  - There is no true animal model for PTLDS or "chronic Lyme" because the symptoms are subjective and the animals can't tell you if they have e.g. fatigue or joint pain.
  - More here: https://www.cdc.gov/lyme/pdfs/PersistenceTranscript.pdf
    https://www.cdc.gov/lyme/pdfs/PersistenceWebinarSlides.pdf

Treatment

- These findings have led to controversy in the lay community regarding human Lyme disease, though there is a strong consensus within the medical community regarding antibiotic therapy.


Government of Canada / Gouvernement du Canada

For health professionals: Lyme disease

On this page


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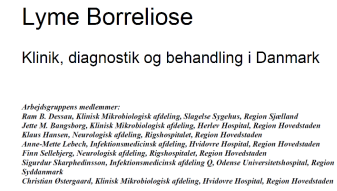
AWMF-Register Nr. 013/044 Klasse: S2k

Leitlinie der Deutschen Dermatologischen Gesellschaft


Lyme Borreliose

Klinik, diagnostik og behandling i Danmark

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Kutane Lyme Borreliose

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Médecine et maladies infectieuses


Lyme borreliosis treatment

DANIELA VAŇOUSOVÁ & JANA HERCOGOVÁ
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Médecine et maladies infectieuses 46 (2016) 343–345

Éditorial

Position de la Société de pathologie infectieuse de langue française à propos de la maladie de Lyme

Lyme disease: The French Infectious Diseases Society's statement

La maladie de Lyme fait l'objet d'une médiatisation importante. De nombreux articles et émissions de radio et de télévision ont contribué à renforcer un sentiment d'état d'alerte concernant cette maladie. L'une des demandes principales des patients est de bénéficier d'une reconnaissance et d'une prise en charge adaptée de leur infection.

les pays. L'incidence en France est évaluée à 43/100 000 habitants sachant que dans certaines régions (Est, Limousin), cette incidence peut atteindre 200/100 000 donc parmi les taux d'incidence les plus élevés en Europe et dans le monde. Dans ces conditions, on ne peut pas parler de chiffres discordants par rapports aux autres pays européens.

Experts from a dozen countries agree, also Sweden, Finland, Norway, Netherlands, Poland, Slovenia, Switzerland

Persistent Non-Specific Symptoms

- 4 notable randomized human trials regarding prolonged antibiotic therapy for Lyme have been published. They reached similar conclusions.
- New England Journal of Medicine 2001
- Neurology 2003
- Neurology 2008
- New England Journal of Medicine 2016

TWO CONTROLLED TRIALS OF ANTIBIOTIC TREATMENT IN PATIENTS WITH PERSISTENT SYMPTOMS AND A HISTORY OF LYME DISEASE

MARK S. KLEMPNER, M.D., LINDEN T. HU, M.D., JANINE EVANS, M.D., CHRISTOPHER H. SCHMID, PH.D., GARY M. JOHNSON, RICHARD P. TREVINO, B.S., DELONA NORTON, M.P.H., LOIS LEVY, M.S.W., DIANE WALL, R.N., JOHN MCCALL, MARK KOSINSKI, M.A., AND ARTHUR WEINSTEIN, M.D.

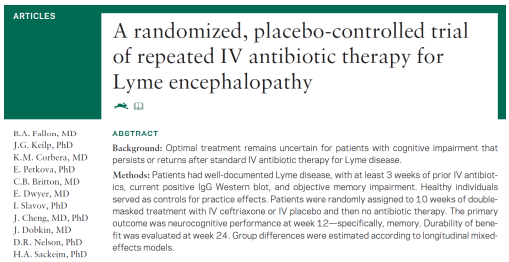
Vermont Department of Health

Persistent Non-Specific Symptoms (continued)

CME **Study and treatment of post Lyme disease (STOP-LD)**

A randomized double masked clinical trial

L.B. Krupp, MD; L.G. Hyman, PhD; R. Grimson, PhD; P.K. Coyle, MD; P. Melville, RN; S. Ahnn, PhD; R. Dattwyler, MD; and B. Chandler, MPA



ARTICLES

A randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy

B.A. Fallon, MD
J.G. Keilp, PhD
K.M. Corbera, MD
E. Petkova, PhD
C.B. Britton, MD
E. Dwyer, MD
I. Slavov, PhD
J. Cheng, MD, PhD
J. Dobkin, MD
D.R. Nelson, PhD
H.A. Sackeim, PhD

ABSTRACT

Background: Optimal treatment remains uncertain for patients with cognitive impairment that persists or returns after standard IV antibiotic therapy for Lyme disease.

Methods: Patients had well-documented Lyme disease, with at least 3 weeks of prior IV antibiotics, current positive IgG Western blot, and objective memory impairment. Healthy individuals served as controls for practice effects. Patients were randomly assigned to 10 weeks of double-masked treatment with IV ceftriaxone or IV placebo and then no antibiotic therapy. The primary outcome was neurocognitive performance at week 12—specifically, memory. Durability of benefit was evaluated at week 24. Group differences were estimated according to longitudinal mixed-effects models.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 31, 2016 VOL. 374 NO. 13

Randomized Trial of Longer-Term Therapy for Symptoms Attributed to Lyme Disease

Anneleen Berende, M.D., Hadewych J.M. ter Hofstede, M.D., Ph.D., Fidel J. Vos, M.D., Ph.D., Henriët van Middendorp, Ph.D., Michiel L. Vogelaar, M.Sc., Mirjam Tromp, Ph.D., Frank H. van den Hoogen, M.D., Ph.D., A. Rogier T. Donders, Ph.D., Andrea W.M. Evers, Ph.D., and Bart Jan Kullberg, M.D., Ph.D.

Vermont Department of Health

New England Journal of Medicine 2001

- 115 patients
  - 57 with positive IgG Western Blot
  - 58 with history of EM but negative serology
  - 1 or more: diffuse MSK pain, cognitive impairment, radicular pain, paresthesias or dysesthesias
  - All had been previously treated
- Randomized into 2 groups
  - Treatment: 30 days IV ceftriaxone then 60 days PO doxycycline
  - Placebo: 30 days IV dextrose then 60 days PO placebo

Seronegative patients required to have documentation of EM rash by physician

New England Journal of Medicine 2001

- Results
  - Primary outcome: improvement in Quality of Life

    [https://www.rand.org/content/dam/rand/www/external/health/surveys_tools/mos/mos_core_36item_survey.pdf]
  - Measured at 30, 60, 180 days
  - Trial stopped when interim analysis of 115 patients at 180 days showed no significant difference

Quality of life measured by Medical Outcomes Study Short-Form General Health Survey (SF-36)

Neurology 2003

- 55 patients
  - History of physician documented EM or late Lyme disease with positive serology
  - Severe fatigue (score >4) on Fatigue Severity Scale
  - All treated with standard therapy within past 6 months
- Randomized into two groups:
  - 28 days IV ceftriaxone
  - Placebo

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Modified version of fatigue severity scale is one of the figures in the article

Neurology 2003

- Results at 6 months
  - Primary outcomes
    - 1. change in score on fatigue scale
    - 2. cognitive speed/impairment as measured by A-A Test
    - 3. clearance of OspA Ag in CSF
  - Fatigue
    - 9.1% improvement in the placebo group: mean score 5.5
    - 22.1% improvement in ceftriaxone group: mean score 4.4
  - No significant difference in cognitive or biologic outcomes

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Alpha arithmic test (reaction time)

Neurology 2003

- Should we prescribe ceftriaxone?
  - Is the improvement in fatigue clinically significant?
    - Antibiotic group still >4 (severe fatigue)
  - 4 of 55 patients (7%) experienced life-threatening adverse events
  - The authors conclude "STOP-LD…suggests that repeated courses of antibiotic treatment are not indicated for persistent symptoms following Lyme disease including those related to fatigue and cognitive dysfunction, particularly in light of the frequency of serious adverse events."

Those are the final words in the paper

Neurology 2008

- 37 patients
  - history of Lyme symptoms
  - positive IgG Western Blot
  - memory impairment
  - already received 3 weeks ceftriaxone
- Randomized
  - 23 received 10 weeks ceftriaxone
  - 14 received IV placebo

Neurology 2008

- Results
  - Primary outcome
    - Neurocognitive performance as measured by index score incorporating motor, psychomotor, attention, memory, verbal fluency
  - At 12 weeks
    - Some improvement in drug-treated group compared to placebo
  - At 24 weeks
    - Improvement was not sustained in the drug-treated group

Neurology 2008

- 26% of ceftriaxone group experienced adverse effects.
- Authors' conclusion:
  - "considering both the limited duration of cognitive improvement and the risks, 10 weeks of IV ceftriaxone…is not an effective strategy for sustained cognitive improvement"

New England Journal of Medicine 2016

- 280 patients
  - History of clinical Lyme disease or positive serology
  - Persistent symptoms attributed to Lyme
    - MSK pain, arthralgia, neuralgia, sensory disturbance, cognitive disturbance, fatigue etc.
  - All received 14 days of IV ceftriaxone initially
- Randomized
  - 12 weeks PO doxycycline
  - 12 weeks PO clarithromycin-hydroxychloroquine
  - 12 weeks PO placebo

Vermont Department of Health

~10% had not been treated so all got CTX initially

New England Journal of Medicine 2016

- Results
  - Primary outcome: quality of life measured by SF-36
  - All 3 groups showed improvement from baseline at 14 weeks
  - No significant difference was found between the study groups

Prolonged Antibiotics

- Theories regarding possible benefits remain untested hypotheses.
- No human trial data shows overall benefit.
- The best current clinical data does not support prolonged courses of antibiotics for post-treatment Lyme disease syndrome.

Consequences of Overdiagnosis and Inappropriate Antibiotic Therapy

Morbidity and Mortality Weekly Report

Serious Bacterial Infections Acquired During Treatment of Patients Given a Diagnosis of Chronic Lyme Disease — United States

Natalie S. Marzec, MD[1]; Christina Nelson, MD[2]; Paul Ravi Waldron, MD[3]; Brian G. Blackburn, MD[4]; Syed Hosain, MD[5]; Tara Greenhow, MD[6]; Gary M. Green, MD[6]; Catherine Lomen-Hoerth, MD, PhD[7]; Marjorie Golden, MD[8]; Paul S. Mead, MD[2]

Death from Inappropriate Therapy for Lyme Disease

A 30-year-old woman died as a result of a large *Candida parapsilosis* septic thrombus located on the tip of a Groshong catheter. The catheter had been in place for 28 months for administration of a 27 month course of intravenous cefotaxime for an unsubstantiated diagnosis of chronic Lyme disease.

Death Due to Community-Associated *Clostridium difficile* in a Woman Receiving Prolonged Antibiotic Therapy for Suspected Lyme Disease

To the Editor—*Clostridium difficile* infections can occur outside the hospital in association with antibiotic use and can result in fulminant colitis and death. In December 2009, the Minnesota Department of Health investigated a death due to *C. difficile* of a 52-year-old woman with no recent hospitalizations.

In June 2009, the patient sought care for symptoms of fatigue, insomnia, achy joints, memory loss, and confusion. These symptoms had been present for >5 years

Vermont Department of Health

Neoplasms Misdiagnosed as "Chronic Lyme Disease"

Clinical features of Lyme disease include erythema migrans rash, facial palsy, arthritis, and peripheral neuropathy. In endemic areas, patients with erythema migrans can be diagnosed clinically. Otherwise, diagnosis is based on the history of possible exposure, compatible clinical features, and positive 2-tier serologic testing.[1]

Chronic Lyme disease is a loosely defined diagnosis given by a small number of physicians—who are not usually infectious disease experts—to patients with various nonspecific symptoms, including patients with no objective evidence of Lyme disease.[2] In addition to adverse outcomes from unconventional treatments for chronic Lyme disease,[3,4] patients misdiagnosed with chronic Lyme disease may be harmed when their actual condition remains untreated.

We report 3 cases in which diagnosis of the patients' actual conditions was delayed due to the misdiagnosis of chronic Lyme disease. Institutional review board approval was not obtained for this case series because it did not meet the regulatory definition of research and was outside the scope of institutional review board requirements. All 3 patients gave written informed consent to share their medical records for this case series.

Cancers in brain, stomach and lung

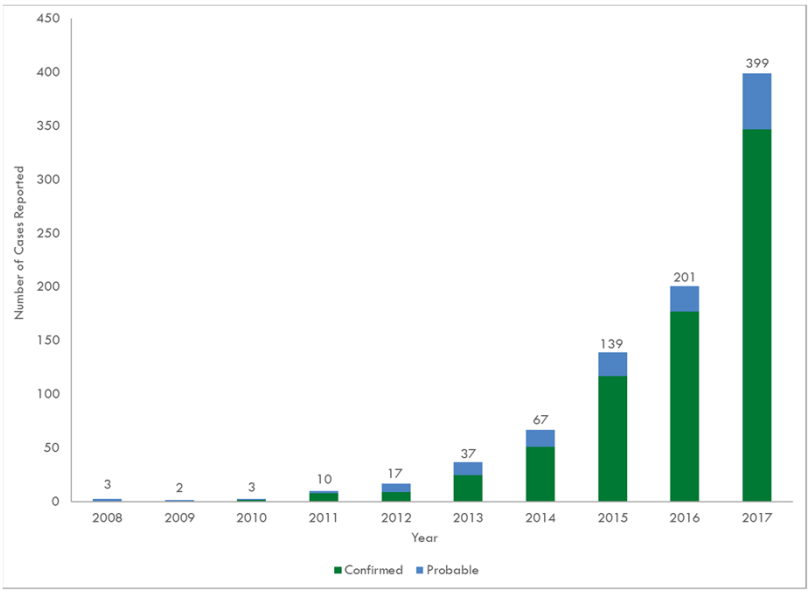
Review

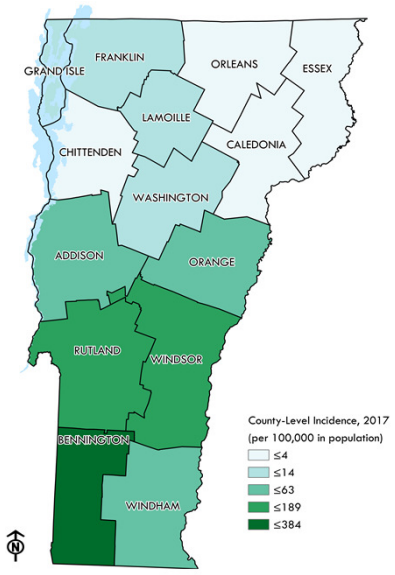
- Even the best available Lyme testing is imperfect and should be interpreted in the context of the patient's clinical presentation. Alternative testing should be carefully scrutinized.
- Lab testing is unnecessary in early localized Lyme presenting with EM rash. Just treat.
- Short courses of therapy (in most cases given PO) remain the standard of care in treating Lyme disease.
- Lyme causes longer-term subjective symptoms in a minority of patients, and although there is some animal evidence of undetermined relevance regarding persistence, current human trial evidence does not support prolonged antibiotic treatment.

Anaplasmosis

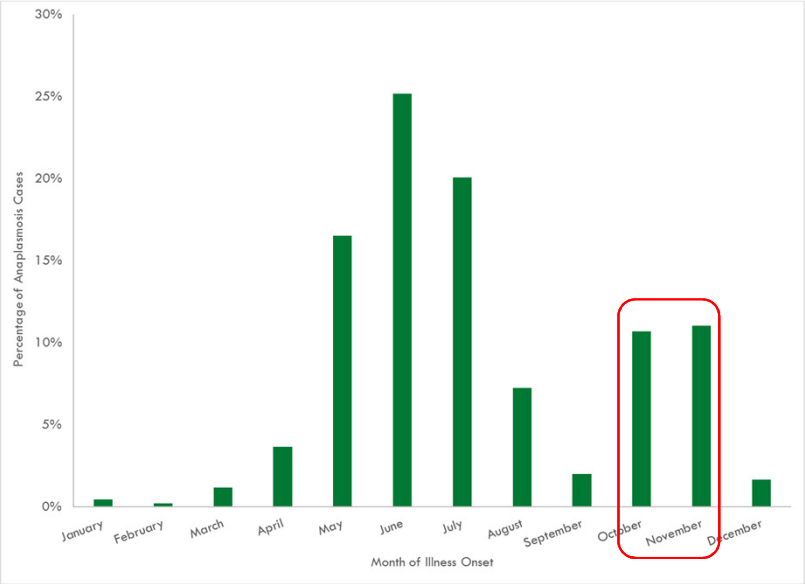
Vermont Department of Health

The Emergence of Anaplasmosis in Vermont



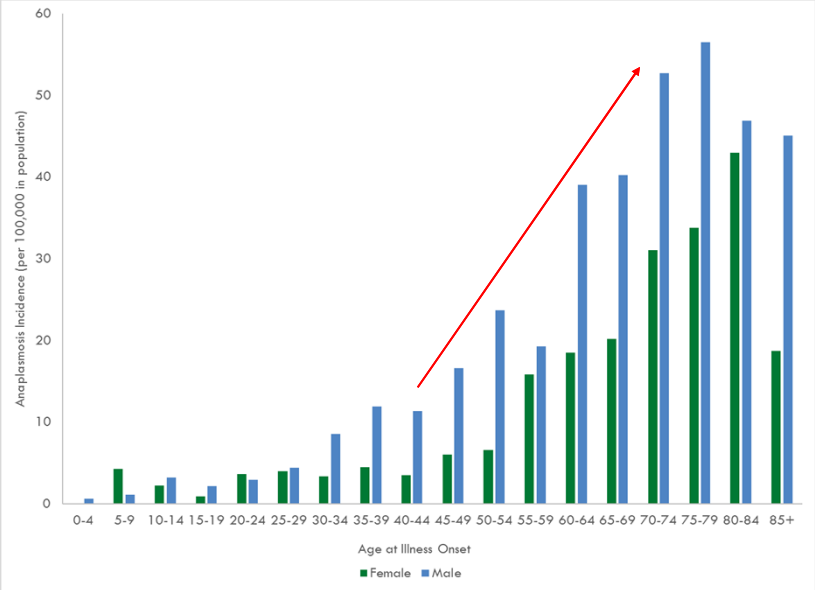


Seasonality of Anaplasmosis in Vermont



- Most cases occur in the spring and summer
- A second smaller, spike in cases occur in the autumn when adult blacklegged ticks are active

Skewed Disease Burden for Anaplasmosis



- Males are at greater risk
- Most cases are in older adults

Diagnosis and Treatment of Tickborne Diseases in Vermont
Part 2:

Anaplasmosis, Babesiosis and *Borrelia miyamotoi*

Dr. Marie J. George

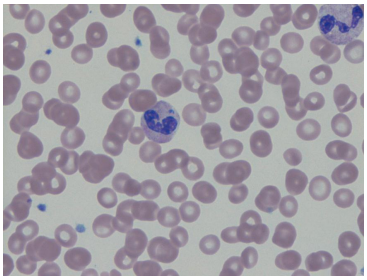
Medical Director, Infectious Disease

Southwestern Vermont Healthcare

VERMONT
DEPARTMENT OF HEALTH

Human Anaplasmosis

- Other name: Human Granulocytic Anaplasmosis (HGA)
- Organism is an obligate intracellular bacteria similar to *Rickettsia*
- First described in 1990s with inclusions seen in granulocytes rather than monocytes (as in ehrlichiosis)



HGA – Clinical presentation

- Acutely ill patient, usually 3-15 days after tick bite (range)
- Fever – often >102 degrees, headache, myalgia-sudden onset
- Rash uncommon <10%
- Meningoencephalitis ~1% – but often severe, associated with ARDS

HGA Clinical

- Range of presentation: asymptomatic – fatal encephalitis or shock/sepsis/acute renal failure/ARDS
- 36% require hospitalization
- PE usually entirely non-localizing but patients acutely ill due to high fever, rigors, headache and malaise

Table 1

Published signs, symptoms, and key laboratory abnormalities (%) reported among laboratory-confirmed human granulocytotropic anaplasmosis (HGA) in the USA, Europe, and in Asia (N = 68 to 794 across features).

Frequency of complaint	**Symptom, Sign, or Laboratory Abnormality (number patients evaluated)**	**Median % (IQR)**
Common	Fever (794)	100 (90-100)
	Malaise (391)	97 (90-98)
	Headache (648)	82 (64-93)
	Myalgia (789)	76 (67-87)
	Arthralgia (661)	56 (27-69)
	Elevated serum ALT or AST (397)	83 (63-98)
	Thrombocytopenia (566)	75 (61-91)
	Leukopenia (566)	55 (47-71)
Less common	Stiff neck (64)	45 (34-48)
	Nausea (521)	39 (35-49)
	Cough (523)	29 (20-30)
	Elevated serum creatinine (199)	49 (25-71)
	Anemia (198)	28 (6-44)
Uncommon	Diarrhea (317)	21 (13-28)
	Vomiting (312)	20 (19-29)
	Confusion (470)	17 (17-18)
	Rash* (489)	6 (3-10)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; IQR: interquartile range
**Erythma migrans where described.*

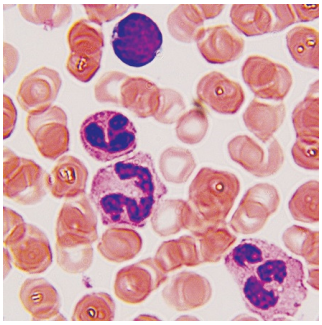
Bakken, JS; Dumler, JS (2015). Human Granulocytic Anaplasmosis. *Infect Dis Clin North Am.* 2015 Jun; 29(2): 341–355. doi: 10.1016/j.idc.2015.02.007

HGA Laboratory

- Leukopenia (may not be present on presentation and occur after hospitalization)
- Thrombocytopenia
- Leukocytosis with left shift – **high WBC does not rule out anaplasmosis!
- Hepatitis (primarily transaminitis, alk phos can be moderately elevated)
- Renal insufficiency/pre-renal azotemia

HGA Laboratory

- Wright stain or Giemsa stained peripheral blood smears demonstrate intracytoplasmic morulae in neutrophils – not the usual way to diagnose but may be high yield in 1st week of illness
- **PCR in blood or CSF from acutely ill patient highly sensitive and specific**
- Acute and convalescent serology (IFA) indicates four-fold rise
  - IgG most sensitive
  - IgM less sensitive for diagnosis of acute infection (use PCR)



Immune Suppression Due to HGA

- Secondary opportunistic infections can occur simultaneously or following HGA – fungal infections *(candida)*, other bacterial infections (strep, staph)
  - Secondary infections are associated with high fatality
- Patients at greatest risk of secondary infection – elderly, immunosuppression, chronic inflammatory or neoplastic illness

Treatment

- Tetracycline antibiotics are drugs of choice and every effort must be made to use them. Be wary of reports of "allergy." This is rare; treat nausea preemptively with antiemetics
- Although some patients can resolve infection without antibiotics, recommended to treat all patients
- **Start prescription before testing is finalized**

Table 4
Recommended antibiotic treatment of HGA

Antibiotic drug	Patient age (years)	Antibiotic dose	Duration (days)
Doxycycline hyclate	≤ 8	2.2 mg/kg 2 times daily IV[a] or PO[b]	4 - 5[c]
	> 8	100 mg 2 times daily IV or PO	10 - 14[d]
Tetracycline HCl	> 8	500 mg 4 times daily PO	10 - 14
Rifampin	Pediatric[e]	20 mg/kg/d (max. 600 mg) in 2 divided doses PO	5 - 7[f]
	Adult[g]	300 mg 2 times daily PO	5 - 7

[a]Intravenous administration;
[b]Oral administration,
[c]Until fever has resolved and three additional days;
[d]14 days recommended if suspected co-incubating *B. burgdorferi* infection;
[e]Individuals aged 16 years or less;
[f]Short duration since therapy not directed towards co-incubating *B. burgdorferi* infection;
[g]Individuals aged 18 years or older.

Bakken, JS; Dumler, JS (2015). Human Granulocytic Anaplasmosis. *Infect Dis Clin North Am.* 2015 Jun; 29(2): 341–355. doi: 10.1016/j.idc.2015.02.007

HGA Treatment

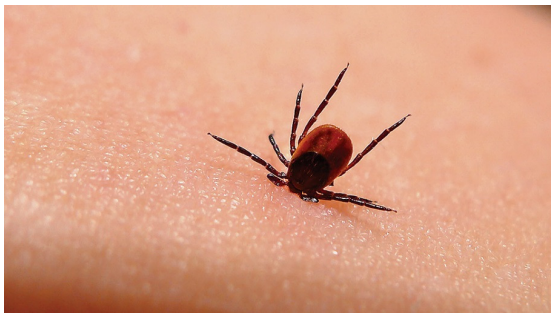
- Prescribe doxycycline to children or pregnant women with HGA **regardless of age**; Continue doxy for 48 hours after resolution of fever (usually 5-7 days) – especially if serious infection.
- Rifampin – second line therapy. Consider use with pregnancy, young children who are not seriously ill. Must follow for full resolution and no relapse

HGA Outcomes

- Most resolve fever and feel greatly improved after 1-2 doses of doxycycline. Short hospital stays, hepatitis resolves within days-weeks. Leukopenia and thrombocytopenia should improve after 24 - 48 hours of treatment
- Death 0.1 - 1.2%
- Complicating ARDS, ARF, encephalitis, neuropathy
- Unclear if protective antibodies develop for second infection (*personal note: I had a patient in 2017 who had infection and full prescription of doxy; second infection 3 weeks later*)

HGA Coinfection With Other Tickborne Infections

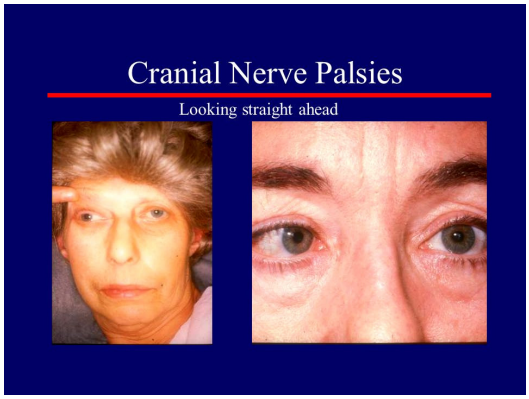
- Any of the infections caused by *Ixodes* can be acquired at the same time as *Anaplasma*
- Coinfection cases in the USA:
  - *Anaplasma* and Lyme (present in 2-11.7% of patients)
  - *Anaplasma* and babesiosis
  - *Anaplasma* and *Borrelia miyamotoi*



HGA and Peripheral Neuritis

Peripheral nerve problems can occur after original infection – usually occur after symptoms of *Anaplasma* have resolved:

- Cranial nerve palsies
- Brachial plexopathy
- Demyelinating polyneuropathy, myelitis

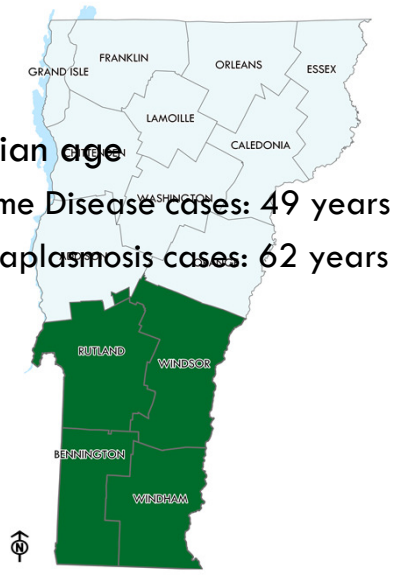


Babesiosis

Vermont Department of Health

Babesiosis in Vermont

- Only 63 cases reported in Vermont (2008-2017)
- Cases more common in older adults
  - Range: 9 – 83 years
  - Median age: 63 years
- ~70% of cases get sick June-August
- ~30% of cases are hospitalized
- Cases have predominately been reported from southern Vermont
- Median age
  - Lyme Disease cases: 49 years
  - Anaplasmosis cases: 62 years



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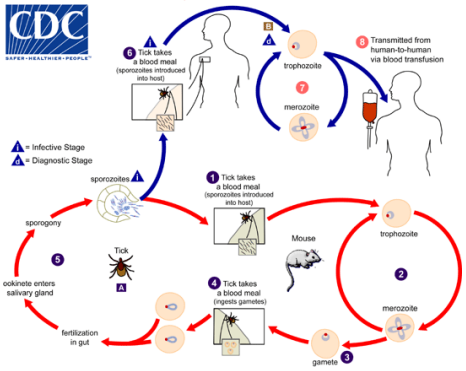
Babesiosis

- A protozoan parasite that infects erythrocytes. It is an obligate intracellular pathogen
- Human illness in Vermont is caused by *Babesia microti*

Babesia Life Cycle

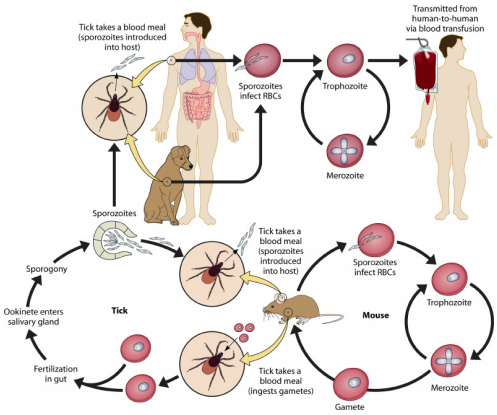
- Ticks inject sporozoites into humans and target RBCs (do not need liver phase)
- Infected RBCs (trophozoites) circulate through organs, including spleen
- Parasite matures and grows inside RBC, replication by budding.
- One ring → two "figure 8"
- Two rings → tetrad "Maltese Cross"



- After division, merozoites destroy RBCs; seek new RBC cells to invade cycle of intracellular infection

Babesiosis - Other Modes of Transmission

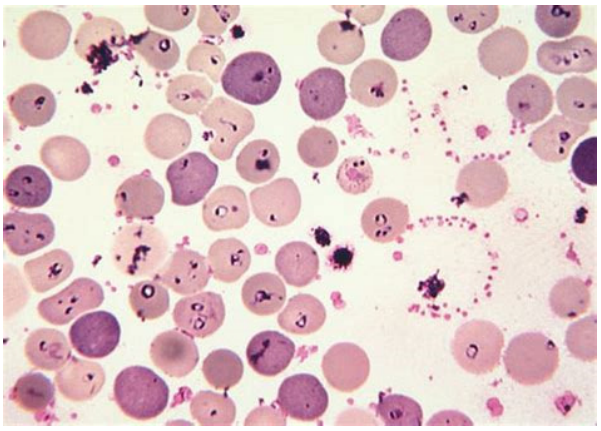
- Blood supply now screened, in several states, including Massachusetts
- Blood transfusion – Most common transfusion-related infection in U.S.
- Transplacental – 1/5 - fatal outcome, rare, case report



Esch, Kevin J.; Petersen, Christine A.; Transmission and Epidemiology of Zoonotic Protozoal Diseases of Companion Animals. Clin Microbiol Rev. 26(1):58-85 · January 2013
DOI: 10.1128/CMR.00067-12

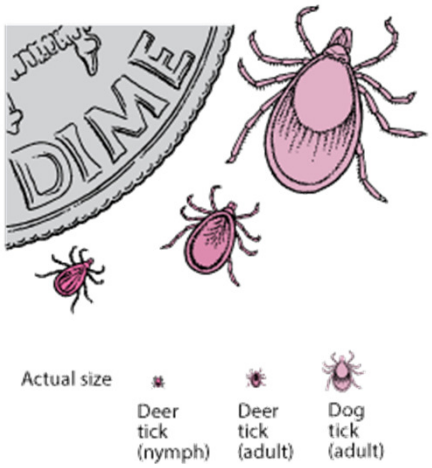
Babesiosis - Clinical

- Range:
  - Asymptomatic
  - Mild, moderate disease
  - Severe infection (hemolysis/death)



Babesiosis - Clinical: Asymptomatic

- Healthy hosts
- Low parasitemia (seroprevalence in New England is highest rate in U.S. Range 0.5-16% Block Island, Nantucket)
- Self-limited, but until resolved host can transmit by blood donation



Babesiosis - Clinical: Mild-Moderate Disease

- 1-4 weeks after bite or 1-9 weeks (or up to 6 months) after transfusion
- Malaise, fatigue, fever, anorexia, nausea, nonproductive cough, arthralgia
- Less common symptoms: hyperesthesia, sore throat, abdominal pain, conjunctival infection, weight loss, photophobia
- PE: hepatomegaly, splenomegaly, red throat, jaundice, retinopathy in infants. Rash is RARE (If present, look for coinfection with another tickborne illness)

Table 1
Symptoms of Babieosis

Symptom	Outpatient (n=41)	Inpatient (n=173)	Total (n=214)
Fever	68	89	85
Fatigue	78	79	79
Chills	39	68	63
Sweats	41	56	53
Headache	75	32	39
Myalgia	37	32	33
Anorexia	25	24	24
Cough	17	23	22
Arthralgia	31	17	18
Nausea	22	9	16

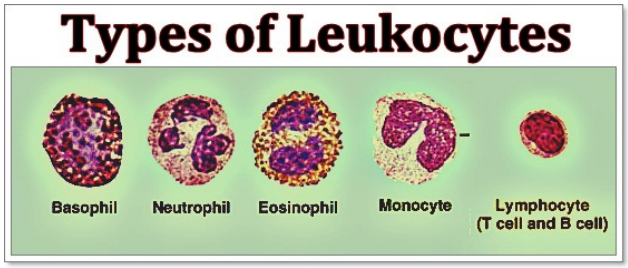
Outpatient cases are from Ruebush et al. and Krause et al. Inpatient cases are from White et al. and Hatcher et al.

Babesiosis - Clinical: Severe Disease

- Usually >50 years old, immunocompromised, pregnant or splenectomized
- *B. divergens* associated with more severe infection
- ARDS, hemolytic anemia, CHF, DIC, renal failure, prolonged relapsing infection
- Death - 10% of hospitalized patients – higher if acquired with pregnancy, transfusion or if previously splenectomized

Babesiosis - Laboratory

- Signs of hemolysis-decreased Hgb and Hct, increased LDH
- Low leukocyte count
- Low platelets (2nd most common lab abnormality)
- Renal failure
- Blood peripheral smear may show organisms incidently in RBCs



Babesiosis - Diagnosis

- Epidemiology of travel to endemic area or transfusion within last 6 months
  - Tick exposure may not be reported
- Thin blood smear (Wright or Giemsa stained)
  - Ring forms (early infection)
  - No hemozoin in rings
  - No gametocytes
  - Tetrads present
- PCR - BOTH sensitive and specific
- Serology – fourfold rise in IgG after four weeks - confirms recent infection; single IgG does not distinguish old from new infection

Babesiosis - Relapsing Infection

- Occurs in patients with immunosuppressive disease, elderly, splenectomy, HIV infection. Can occur in healthy patients
- May have positive PCR which is persistently positive or became negative then positive again
- May require 6 plus weeks of antimicrobial therapy – alternative regimens noted in treatment section
- Close clinical follow-up: repeat smears, repeat PCRs to confirm resolved infection

Babesiosis - Treatment

- Asymptomatic
  - If PCR positive or blood smears positive
  - Do not prescribe for single positive serology only
  - 7 days atovaquone and azithromycin
- Mild-Moderate
  - Atovaquone and azithromycin: 7-10 days (preferred) or clindamycin and quinine
  - Adverse reactions: 15% atovaquone and azithromycin; 72% clindamycin and quinine
- Severe
  - Clindamycin and quinine (can give oral or IV)
  - +/- exchange transfusion (parasitemia >10%; severe anemia Hgb<10g/dl or/+ liver/renal failure
- Relapsing
  - Treat up to 6 weeks with clindamycin and quinine, atovaquone /proguanil, clindamycin and doxycycline, azithromycin and doxycycline, artemisinin, atovaquone and doxycycline, atovaquone/azithromycin and clindamycin

Babesiosis - Treatment

Table 2
Treatment of human babesiosis

Antimicrobials	Dose	Frequency
Atovaquone plus azithromycin		
Atovaquone	Adult: 750 mg	Every 12 hours
	Child: 20 mg/kg (maximum 750 mg/dose)	Every 12 hours
Azithromycin	Adult: 500 to 1000 mg	On day 1
	250 to 1000 mg	On subsequent days
	Child: 10 mg/kg (maximum 500 mg/dose)	On day 1
	5 mg/kg (maximum 250 mg/dose)	On subsequent days
Clindamycin plus quinine		
Clindamycin	Adult: 600 mg	Every 8 hours
	Child: 7-10 mg/kg hours (maximum 600 mg/dose)	Every 6-8
	Intravenous administration	
	Adult: 300-600 mg	Every 6 hours
	Child: 7-10 mg/kg hours (maximum 600 mg/dose)	Every 6-8 hours
Quinine	Adult: 650 mg	Every 6-8 hours
	Child: 8 mg/kg (maximum 650 mg/dose)	Every 8 hours

All antibiotics are administered by mouth unless otherwise specified. All doses administered for 7 to 10 days except for persistent relapsing infection.

Vannier, Edouard G.; Diuk-Wasser, Maria A.; Mamoun, Choukri Ben; and Krause, Peter J. "Babesiosis." Infect Dis Clin North Am. 2015 Jun; 29(2): 357–370. doi: 10.1016/j.idc.2015.02.008

Borrelia miyamotoi

Vermont Department of Health

Newly Recognized Tickborne Disease in Vermont

- First cases in Vermont were reported in 2016
  - 2016: 7 cases
  - 2017: 13 cases
- Case Characteristics (n = 20)
  - Age:
    - Range: 4 – 80 years
    - Median: 64 years
  - Gender: 50% female
  - Illness onsets range from May – October
  - 20% of cases have been hospitalized

- 2016: 7 cases
- 2017: 13 cases

Borrelia miyamotoi General

- It is not a true relapsing fever pathogen
- IS NOT: fever – resolution - sudden hypotension fever/severe symptoms
- IS: fever, HA, malaise – resolution - recurrences of same symptoms. "Relapsing fever-like illness"

Borrelia miyamotoi Identification/Diagnosis Difficulties

- Genetically related to *B. burgdorferi* species, and shares 4 of 10 antigens with Lyme *Borrelia*

Distinctive illness

Difficulty with cross reactivity on antigen and antibody assays

- No animal model
- Serology has false negatives
- Low numbers of clinical cases

Vermont Department of Health

B. miyamotoi Clinical case series: Russia 2011

- 64 cases
- Fever, fatigue, headache – greater than 90%
- "Relapsing" fever 11% – 2-3 episodes, each lasted 2-5 days, mean 9 days between.
- Rash – rare, EM-like – 4%
- Patients had positive PCR for *B. miyamotoi*, also had increased serology for Lyme
- Elevated LFTs common – 68%
- Most did not have cytopenias

(Platonov, et al. *Emerging infectious Disease* 2011 Oct; 17(10): 1816–1823)

B. miyamotoi Clinical Features/Epidemiology

Other case series:

- Chowdri, et al. *Annals of Internal Medicine* 2013. 159: 21-7
- Hovius, et al. *Lancet* 2013. 382: 658
- Safo, et al. *Emerging infectious Disease* 2014. 20:1391-4
- Malloy, et al. *Annals of Internal Medicine* 2015. 163: 97-8

Table 2

Comparison of symptoms reported from U.S. and Russian patients.

Symptom	US (n = 51)	Russia (n = 46)
Fever, chills	96%	98%, 35%[a]
Headache	96%[b]	89%
Myalgia	84%	59%
Arthralgia	76%	28%
Malaise/fatigue	82%	98%
Rash/EM[c]	8%	9%
Gastrointestinal symptoms[d]	6%	30% (nausea)
		7% (vomiting)
Respiratory symptoms[e]	6%	na[f]
Neurological symptoms (dizziness, confusion, vertigo)	8%	na
Stiff neck	na	2%

[a]Fever and chills were reported in separate categories.
[b]Authors noted in most patients the headaches were severe.
[c]US patients were described as having a rash. Russian patients were noted for having a single erythema migrans.
[d]For US patients, GI symptoms included nausea, abdominal pain, diarrhea, anorexia. For Russian patients, GI symptoms included nausea and vomiting.
[e]Labored breathing or short of breath.
[f]Not reported.

Reference: Stone & Brissette. *Frontiers in Immunology* 2017. Jan 19, 8:12

B. miyamotoi Clinical - Important Observations

- At least one person has resolved infection without meds
- Transmission in blood transfusion has been demonstrated in mice. No human cases described yet
- Meningoencephalitis described in U.S. patients: progressive decline of cognition, gait unsteadiness over weeks to months, no fever

B. miyamotoi Clinical - Important Observations

- Clinical experience in Bennington – patients may be sick enough to be admitted, acutely ill over several days - 2 weeks, younger persons sicker but report lower fever, confusion prevalent, similar to anaplasmosis, LFTs always elevated, cytopenia +/-
- Cases of meningoencephalitis were prominent and severe in patients with immunocompromised conditions (lymphoma, use of Rituximab, neutropenia)

Borrelia miyamotoi - Diagnosis

- Serologic testing of antibody to glpQ specific antibodies by 2 tier tests (IgG) 4 weeks apart – NOT preferred for acute illness, OK for look back
- 10% of *Borrelia miyamotoi* cross-reacted with *Borrelia burgdorferi* in study by Krause et al., *Emerging Infectious Disease* 2014. 20: 1183-90
- Therefore PCR is the preferred method to differentiate the two infections acutely and serology can look back more specifically for *Borrelia miyamotoi*

Borrelia miyamotoi Diagnosis

- Look for specific comment notation when ordering "*Borrelia* PCR"
- Testing lab may indicate "Positive for *Borrelia*," then indicates species detected
  - *Borrelia miyamotoi* will be present anytime there is an active, untreated infection

Borrelia miyamotoi Treatment

- Treatment is based on clinical series and case reports. Devised due to comparison with other *Borrelia* infections
- No trials for duration, dose, type of antibiotics
  - Doxycycline 100g every 12 hours for 7-14 days in normal adults with acute infection
  - Ceftriaxone 2-4 weeks or PCN G. 24mu per day for 4 weeks - meningoencephalitis
  - Amoxicillin, cefuroxime – similar to Lyme treatment (use for intolerance of doxycycline, children under age 8, pregnant women)
  - Jarisch-Herxheimer reported in Russian series in 15% of patients, sometimes severe with hypotension

Vermont Department of Health

Thank You

- Thank you for viewing the course material
- Please return to the Health Department website (www.healthvermont.gov/TickborneDiseaseCME) to apply for continuing education credits through the Vermont Area Health Educations Centers (AHEC)
- Comments or questions? Please contact Bradley.Tompkins@vermont.gov