Presentation Goals
- Short-term: increase understanding of Lyme
  - Improve knowledge base
  - Fill in gaps, correct misconceptions
- Long-term: improve patient care
  - Improved diagnostic skills
  - Patient-centered care

Conflict of Interest Disclosure:
President of Partnership for Healing and Health, Ltd.
Provides continuing medical education courses on tick-borne diseases

Importance
- Lyme is not Rare
  - Most common vector-borne illness in US
  - Severe/chronic illness for some
  - Risk higher than thought
    - Surveillance case reports
    - CDC: > 300,000 new cases annually

Nor is it Trivial
- Significant disability and lost production
  - National survey of Lyme patients with chronic disease
    - 65% cut back or quit school/work
    - 26% received disability payments
- Patient costs vary; often high
  - $4000 – ave, for all cases
  - > $16,000 for late cases
- Limited access to care
  - Few providers care for sickest
  - Patients leave community for care

Johnson L. Peer J 2015;2:e282
Vector-borne

- Black-legged ticks and *Borrelia burgdorferi*
- Feedings - once per stage
  - Reservoir hosts: Mice, shrew, chipmunks
  - Perpetuate infection locally
  - Incidental hosts: Humans, pets, horses
- Acquire/transmit bacteria
  - Once infected, always infected

Transmission Risk of Known Bite

- "Average Risk" uninformative
- Risk = Tick infection rate x Transmission rate
  - Transmission rate based on tick attachment time
    - Attachments < 24 hours: transmission unlikely

Example:
- Tick attached for 60 hours
- 30% ticks in area infected
- 60 hrs attach = 50% trans rate
- 50% x 30% = 15% risk of transmission

Zoonotic Pathogen

- Zoonotic = adaptive
  - Modulates and controls host responses
  - Multiple mechanisms to evade/modulate immune system
  - Facilitates bacterial persistence
- Family of bacteria: *Borrelia burgdorferi sensu lato*
  - Several pathogenic species
  - U.S.: *B. burgdorferi sensu stricto*
  - > 100 strains
  - Species/strain differences impact
    - Presentation, diagnosis, treatment

Structure and Form

- Genome
  - 1 chromosome and 21 plasmids
- Outer surface proteins (Osps)
  - Different types, different functions, vary with environment
  - Trigger antibody response
    - Basis for serologic testing

Pleomorphic

- Mobile
- "Cyst"
- Able to switch between forms
  - "Cyst" or cell-wall deficient form
    - Response to environmental changes
    - Clinical significance unstudied
      - Potential significance: 1) Enhanced survival - immune evasion, antibiotic tolerance
      - 2) Serology criteria inapplicable

Co-infections

- Other pathogens transmitted by black-legged ticks
  - Single bite may cause multiple infections
  - Complicate diagnosis and treatment
- Blacklegged Tick Transmitted Diseases
  - Lyme
  - Powassan encephalitis
  - Anaplasmosis
  - B. miyamotoi disease
  - Babesiosis
  - Bartonellosis
  - Ehrlichia muris-like disease
Lyme: A Clinical Diagnosis

Lyme evaluation – same approach as other disease evals

- General history, plus
  - Lyme-specific questions investigate
    - Known and potential tick exposures
    - Hx of known bites or co-infections
    - Live, work, recreate, travel
    - FH of tick-borne diseases
  - Questions investigating other diagnoses in differential
    - PMH; current illnesses/conditions; + FH
- Exam – targeted
  - Symptom-driven; also skin, joints, neuro
- Lab augments, doesn’t overrule

Risk in Texas

- Reported cases
  - 2010 - 2013: 373
- Tick survey findings*
  - 50% deer ticks infected*

Lyme Disease Basics

- Two distinct stages
  - Not every patient exhibits both
  - Antibiotics required
- Early: localized in skin
  - +/- systemic symptoms/findings
- Late: dissemination to other sites

Recognizing Lyme Clinically

- Pattern recognition: we see what we know
  - How Doctors Think by Jerome Groopman, MD
- Symptoms and findings differ by stage
  - Multi-systemic
  - Nonspecific
  - Variably present
    - Differ patient to patient
    - Relapsing/remitting pattern

Nonspecific Symptoms have Value

- Contribute to diagnostic pattern
- Common in both stages
  - Early Lyme
    - Fever, chills, malaise, headache, stiff neck, paresthesias, arthralgia, myalgia, sore throat, dry cough
      (Steere A. Am J Med 2003)
  - Late Lyme: wide range
    - Fatigue, headache, pain, sensory changes, irritability, depressed mood, sleep disturbances, word searching, hearing loss
      (Logigian EL. N Engl J Med 1990)
Early Disease
- Onset 2-30 days post-bite
- Multiple presentations
  - Asymptomatic
  - "Flu-like" illness
- Serologic testing not recommended
- Antibiotics required

Other Manifestations
- Symptoms: fever, chills, malaise, headache, stiff neck, arthralgia
- Findings: lymphadenopathy, pharyngeal erythema
- Differential: allergic reactions, insect or spider bites, bacterial cellulitis, contact dermatitis, tinea

Disseminated Disease
- Multiple EM
  - Return of bacteria to skin; often < 5cm
- Facial nerve palsy
  - 25-50% peds cases in endemic areas
  - Bilateral FN palsy: Lyme until proven otherwise
  - Predictive pattern of Lyme:
    - Onset June-Oct.
    - Fever, HA, no herpetic lesions

Late Disease
- Symptoms widespread
- Checklists of common symptoms
  - Pattern recognition easier
  - Follow-up info
  - Reaffirm diagnosis
  - Monitor treatment response

Meningitis
- Smoldering; more like aseptic than bacterial
- Predictors: "Rule of 7s" (all 3)
  - > 7 days of headache
  - > 70% mononuclear cells in CSF
  - Cranial nerve palsy

Carditis
- AV conduction delays most common; myo-, epicarditis
- Dizzy, palpitations, chest pain, SOB, CHF symptoms
- Abnormal pulse, hypotension, rales, JVD, pedal edema, pericardial rubs
Arthritis
- Months – years post-bite
- 60% of previously untreated
- Multiple brief episodes
- Knee most common
  - Small joints occasionally

Late Neurologic
- Months – years post-bite
- True incidence unknown
- Presentation types
  - Peripheral neuropathy
    - Sensory
    - Motor
  - Autonomic neuropathy
  - Encephalopathy
  - MS-like, Parkinson-like
  - Neuropathic pain
- Motor neuron disease
- Cerebellar syndromes
- Dementia
- Neuropsychiatric conditions
  - Depression
  - Anxiety
  - Bipolar disease

Potential Findings
- Abnormal vital signs
- Skin: rashes, color changes
- Eye abnormalities
- Joint abnormalities
- Sensory changes
- Cognitive disturbances
- Mood alterations
- Muscle weakness
- Tremors
- Gait disturbances
- Balance difficulties
- Reflex changes
  - DTRs
  - Pathologic

Motor Findings
- Muscle weakness
- Tremors
- Gait disturbances
- Balance difficulties
- Reflex changes
  - DTRs

Difficult Diagnosis to Make
- Symptom rich and exam poor
  - Findings can be subtle
  - Detailed neurologic exam critical
  - May need ancillary testing
- Absence of finding ≠ absence of disease
  - Halperin study
- Wide differential

Differential
- Fibromyalgia
- Chronic fatigue syndrome
- RA
- Diabetes
- Degenerative arthritis
- MS
- Vasculitis
- Hypothyroidism
- ALS
- Sarcoidosis
- Psychiatric disorders
- Sleep Apnea
- B12 deficiency
- Heavy metal toxicity
- Anaplasmosis
- Babesiosis
- Bartonellosis
- Ehrlichiosis
- Epstein-Barr virus
- Mycoplasma
- Parvovirus
- West Nile virus
- Syphilis
- Relapsing fever
- B. miyamotoi
Lab: Disease Identification Limited

- Serology - ELISA and Western blots
  - Indirect evidence of exposure
  - Measure antibody levels, not bacteria
- Reliable tests
  - Finds everyone with disease = Sensitivity
  - Negative when disease absent = Specificity
  - Results consistent = Reproducible
- Two-tier Lyme serology frequently unreliable
  - Highly specific (positive tests indicate true disease) BUT
  - Insensitive, not reproducible

Western Blot Criteria Problematic

- Process
  - Labor intensive
  - Tech dependent
- Interpreting band patterns
  - Multiple schemes
  - CDC criteria original intent
    - Identify surveillance cases
    - Restrictive/specific
      - Very rare false positives
      - Many false negatives

CDC Two–tiered Testing Algorithm

<table>
<thead>
<tr>
<th>ELISA</th>
<th>Western Blots</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neg</td>
<td>Pos/ Equiv</td>
</tr>
<tr>
<td>Pos/</td>
<td>Required bands: 2 of 3 IgM* 5 of 10 IgG*</td>
</tr>
<tr>
<td>Equiv</td>
<td>Neg</td>
</tr>
</tbody>
</table>

Reportable Surveillance Case

Meets Surveillance Case Definition

Doesn’t Meet Definition

Two-tier Testing: Problems

- Poor reproducibility/sensitivity
  - Ang 2001: Compared 8 ELISA and 5 WB results
    - Sensitivity of 40 two-tier combinations varied significantly
    - IgG WB agreement: 24 - 84%
    - Conclusion: Choice of ELISA-WB combination highly influences ability to obtain (+) result
- Biased against neuro cases
  - 5 of 10 IgG criteria from Dressler
    - Bands chosen for specificity
  - Prospective study of criteria in Dressler’s patients
    - Sensitivity: 96% arthritis; 72% neuro

Surveillance Case Criteria Misapplied

- (+) Two-tier in symptomatic patient = Lyme
- (-) Two-tier DOES NOT rule out Lyme

Treatment

- Wide range of antibiotic choices
  - Disease stage, severity
  - Patient-centered outcomes and informed consent
- Most successful in early disease
- Expect Failures – patient remains ill
  - High in late neurologic disease
  - ~ 20 -30% for EM*

Dressler F. J Infect Dis 1993; 167(2):392-400
Eng CW. Eur J Clin Microbiol Infect Dis. 2011

Cameron D. Expert Rev Anti Infect Ther Ahead of print 7/30/2014
Evidence-based Options

- Tick bites, any engorgement
  - 100-200 mg of doxycycline, twice daily for 20 days
  - Avoid single dose doxycycline

- EM rashes
  - Amoxicillin 1500-2000 mg daily, BID - TID
  - Cefuroxime 500 mg BID
  - Doxycycline 100 mg twice daily
  - Azithromycin 250-500 mg daily x 21d

(37)

Arthritis, uncomplicated: 28 days
- Doxycycline 100-200 mg twice daily,
- Amoxicillin 500 mg three times daily, or
- Cefuroxime 500 mg twice daily

Persistent arthritis
- Improved but unresolved symptoms:
  - Repeat oral antibiotics for 28 days
- Minimal improvement:
  - Ceftriaxone 2 gm IV for 28 days
- Continued local joint symptoms
  - Synovectomy is an option

(38)

Neurologic disease
- Little evidence to support for any approach
  - Antibiotic options: IV ceftriaxone, oral agents, alone or in combinations, IM penicillin
  - Meningitis or facial nerve palsy: 28 days; reevaluate
    - Doxycycline 300-400 mg po daily
    - Ceftriaxone 2 gm IV daily
    - Encephalopathy/neuropathy: 30 days, reevaluate
    - Doxycycline 300-400 mg po daily
    - +/- other first-line oral agents
  - Severe neuro manifestations: 30 days, reevaluate
    - Ceftriaxone 2 gm IV daily, +/- oral doxycycline

(39)

Arthritis, uncomplicated: 28 days
- Doxycycline 100-200 mg twice daily,
- Amoxicillin 500 mg three times daily, or
- Cefuroxime 500 mg twice daily

(40)

Why Does Treatment Fail?

- Potential Mechanisms
  - Immune dysregulation
  - Auto-immune via molecular mimicry
  - Unregulated inflammatory processes
  - Tissue injury
  - Secondary conditions
  - Untreated co-infections
  - Persistent B. burgdorferi infection
  - Combination of above

(41)

Bacterial Persistence Possible?

Survival Mechanisms
- Induces beneficial host response
- Modulates host immune response
- Alters appearance
  - Changes shape
  - Mobile form changes surface proteins
- Locates outside immune cells reach
- Antibiotic tolerance/persister cells

(42)
**Human Xenodiagnostic Study**
- Assumes
  - Tick salivary chemooattractant attracts Bb to bite site
  - Feeding duration sufficient for Bb to reach tick
- Process
  - Uninfected, unfed ticks put on subject; feed until full
  - Look for Bb in tick by culture and PCR
  - Direct evidence of infection
- 36 subjects
  - 1 with active EM
  - 10 with persistent post-treatment symptom
  - Positive in EM patient and 1 post-treatment patient

**Antibiotic Retreatment Helps Some**
- 4 NIH-funded trials
  - Different patient subgroups, designs
  - Ceftriaxone, varying durations; +/- doxycycline
- Krupp and Fallon
  - Sustained improvement in severe fatigue
  - High adverse event rate
  - Not recommended for all
  - Recommended finding safer antibiotic regimens
- Individualized risk-benefit assessment important

**Now You Know**
- Significant public health problem
- Clinically important aspects of vector, pathogen
- Clinical diagnosis
- Two-tier testing limited clinical usefulness
- Treatment regimens starting points
- Treatment failures occur
- Bacterial persistence occurs
- Antibiotic retreatment may be beneficial

**Safety: Ceftriaxone for 30 or more days**

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Days of IV antibiotic/ placebo*</th>
<th>IV Days*</th>
<th>Significant Adverse Events</th>
<th>All Adverse Events 1000 IVD Days*</th>
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<tbody>
<tr>
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<td>18</td>
<td>30</td>
<td>540</td>
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<tr>
<td>Klempner 2001</td>
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<td>3670</td>
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<td>Krupp 2003</td>
<td>55</td>
<td>30</td>
<td>1650</td>
<td>4 (7.2%)</td>
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<tr>
<td>Fallon 2008</td>
<td>37</td>
<td>70</td>
<td>2590</td>
<td>7 (18.9%)</td>
<td>2.7</td>
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<tr>
<td>Total</td>
<td>239</td>
<td>850</td>
<td>13 (5.4%)</td>
<td>1.5</td>
<td></td>
</tr>
</tbody>
</table>

* Rough estimate; did not account for patients who discontinued therapy due to adverse events

**Selected References**
Lab references

Poor Reproducibility

Poor Sensitivity – ELISA

Poor Sensitivity – Western blots

Two-tier Problematic

Western bird specificity
- High >95%.

IgM > IgG

Post-Rx Serology not Useful


References