Pathogenesis, Transmission and Treatment:

Report to Tick-Borne Disease Working Group

Co-Chairs:
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Tick-Borne Disease Working Group

Meeting #5

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Disclaimer

Information and opinions are those of the presenter(s) and do not necessarily reflect the opinions of Working Group members or the Department of Health and Human Services.

Background

- We reviewed three areas:
  - Pathogenesis:
    - How *B. burgdorferi* infection causes pathology in an infected host
  - Transmission:
    - How *B. burgdorferi* establishes and maintains infection in the host
    - Did not cover other potential forms of transmission
  - Treatment:
    - Early acute, different manifestations and continuing signs and symptoms following treatment
  - Focused solely on *B. burgdorferi*

Subcommittee members

Co-Chairs	Type	Stakeholder Group	Expertise/Specialty
Wendy Adams, MBA - Bay Area Lyme Foundation	Public	Patient Advocate	Research Grant Director; Board member, Lyme Disease Biobank
Estella Jones, DVM - Food and Drug Administration	Federal	Public Health	Acting Deputy Director, Office of Counterintelligence and Emerging Threats

Members	Type	Stakeholder Group	Expertise/Specialty
Nicole Baumgarth, DVM, PhD University of CA Davis	Public	Scientist	Immunology; expertise in mammalian infectious disease immunology animal models
Patricia Coyle, MD - Stony Brook University	Public	Physician	Neurology, Director Multiple Sclerosis Care Center
Sam Donta, MD	Public	Physician	Infectious diseases; Lyme physician (retired)
Brian Fallon, MD - Columbia University	Public	Physician	Neuropsychiatry; clinical trial investigator; Director, Columbia Lyme Disease Center
Lorraine Johnson, JD, MBA - Lymedisease.org	Public	Patient Advocate	CEO Lymedisease.org; Principal investigator, MyLymeData
David Leiby, PhD - Food and Drug Administration	Federal	Public Health	Chief, Product Review Branch, Center for Biologicals Evaluation and Research (CBER)
Elizabeth Maloney, MD- Partnership for TBD Education	Public	Physician	Family medicine; Medical Director, LymeCME- Tick-borne disease physician education
Jon Skare, PhD - Texas A & M University	Public	Scientist	Microbiology; expertise in *B. burgdorferi* host interactions, complement inhibition
Brian Stevenson, PhD - University of Kentucky	Public	Scientist	Microbiology; expertise in *B. burgdorferi* gene/protein expression during infection

Other Participants
James Berger, MS – Designated Federal Officer
John Aucott, MD - Co-Chair of TBD WG
Yanni Wang, PhD – Medical writer

Methods

- Subcommittee meetings
  - 13 meetings held in total
    - 11 speakers presented
      - Subcommittee members (almost all presented)
      - Presenters had substantial expertise in area
        - Microbiology
        - Immunology
        - Animal models
        - Clinicians
  - Data sources utilized:
    - Scientific literature, government websites, patient registries, clinical experience
    - Federal government inventory not provided, therefore no ability to review previous government activities

Methods

- Process:
  - Initially devised key issues
  - Priorities developed from issues
  - Formed one group around each priority
  - Each group authored their own report with input from other members
  - Discussion online and during weekly conference calls about points of interest from presentations, outlines and drafts
- Consensus decision making employed, feedback on each section received and discussed
- All final votes were unanimous

Results – Potential Key Issues

1. Mechanisms of *B. burgdorferi* Persistence in Animal Models	2. Pathogenesis of Continued Signs or Symptoms of Disease	3. Optimal Treatment Regimens	4. Transmission of *B. Burgdorferi*
• Pathogenesis of Bb persistence in animal models • Evidence for efficacy of treatment in eliminating Bb in animal models • Pathogenesis of Bb infection and persistent infection after antimicrobial treatment in humans	• Pathophysiology of Lyme disease signs/symptoms, including persistent infection, immune dysfunction, co-infection, neural dysregulation • Tools/biomarkers to identify mechanisms of continued signs/symptoms • Identification of predictors of disease course	• Potential treatments that address Lyme disease signs/symptoms • Efficacy for current treatment regimen for acute, disseminated and persistent signs and symptoms • Does infection with >1 pathogen change treatment efficacy • Assessing treatment outcome measures	• Mechanisms by which Bb establishes and maintains infection • Evidence for non-tick mediated transmission of Bb • Evidence for vectors other than Ixodes ticks transmitting Bb • Evidence for effects of *Borrelia* subspecies on tick transmission rates

Results - Priorities

1. What mechanisms of *B. burgdorferi* pathogenesis allow it to persist in some animal species despite a competent immune system and/or antimicrobial therapy? (What are the gaps in human research that need to be addressed to explore this model of pathogenesis in humans?)

2. What is the pathogenesis of persistent symptoms in antibiotic-naïve and antibiotic-treated patients? Are there biomarker(s) to determine the continuing presence of infection? (What are the gaps in research regarding ongoing symptoms related to the effect of delayed diagnosis, immune dysfunction, persistent infection, co-infections and neural dysregulation?)

3. What is/are the best treatment regimens for acute Lyme disease, and for patients with ongoing symptoms who have or have not been previously treated? (Gap: What are the tools needed to measure treatment outcomes in Lyme disease, including but not limited to patient-centered outcomes, clinical practice outcomes, and innovative research tools?)

Results and Potential Actions - Priority 1

1. What mechanisms of *B. burgdorferi* pathogenesis allow it to persist in some animal species despite a competent immune system and/or antimicrobial therapy? (What are the gaps in human research that need to be addressed to explore this model of pathogenesis in humans?)

- **Potential actions:**
  - **Promote research on animal models of *B. burgdorferi* infection and the mechanisms of disease processes in humans with an emphasis on pathologies that are currently lacking, e.g., neuroborreliosis**
    - **Insufficient understanding of mechanisms of disease in animal models, and need to understand how applicable these are to human disease**
  - **Pursue further study of mechanisms of *B. burgdorferi* survival during infection processes and its tolerance to antibiotics and other stresses**
    - **Immune system is affected by *B. burgdorferi* to enable establishment and maintenance of infection in immunocompetent hosts**
    - **Animal models and human case studies show that the pathogen may persist after antibiotic treatment**
      - **If *B. burgdorferi* is still present, is that the etiology of continuing signs and symptoms?**

Results and Potential Actions– Priority 2 & 3

2. What is the pathogenesis of persistent symptoms in antibiotic-naïve and antibiotic-treated patients? Are there biomarker(s) to determine the continuing presence of infection?

3. What is/are the best treatment regimens for acute Lyme disease, and for patients with ongoing symptoms who have or have not been previously treated?

Results and Potential Actions – Priority 2 & 3

- **Potential actions:**
  - Conduct clinical trials using more inclusive entry criteria representing the heterogeneity of patients seen in clinical practice and including different treatment approaches
    - Insensitive testing has led to a data set that may not be representative
    - Current data from trials are not generalizable to clinical practice
    - Utilize innovative patient-centered trial designs and big data tools to accelerate research; promote shared medical decision-making in clinical practice
  - Develop and disseminate more comprehensive clinician education that highlights diverse symptomology, expanding geography of infecting ticks, and limitations of current testing procedures
    - Include diverse group of stakeholders, including clinicians, research scientists, and patients that represent the spectrum of scientific and medical expertise and perspectives on Lyme disease

Results and Potential Actions– Key Themes

- Limited knowledge of human pathophysiology impedes patient care, additional research into pathogenesis is needed
  - Animal models useful but no single, well-characterized animal model reflects the spectrum of human disease, e.g., neuroborreliosis
  - Basic mechanisms of immune evasion are not well understood
  - Persistent infection is sometimes seen in vitro, in animals and in humans - does this cause ongoing symptoms in patients?
  - Could understanding molecular mechanisms better inform therapeutic choices?
  - What is the potential role of pro-inflammatory cytokines, *B. burgdorferi* lipoproteins, autoantibodies and cross-reactive antibodies?
  - Do strain variations impact therapeutic outcomes?
  - Does the addition of another pathogen(s) affect the disease process, diagnosis or treatment of the infections?

Results and Potential Actions– Key Themes

- Clinicians need better tools to diagnose and treat patients
  - Lack of direct biomarkers of infection
    - No biomarker for untreated and previously treated infection, or test of cure
    - Lack of biomarkers that can predict risk of failure

- Given the massive improvement in basic science technologies, novel clinical trial design, access to large databases and new data mining techniques, can more effective treatments be identified more rapidly and efficiently?
  - May be most timely way to improve patient care

- Utilize innovative patient-centered trial designs to accelerate research and promote shared medical decision-making in clinical practice

Discussion

- Challenges and Limitations of Report
  - Insufficient length of time to thoroughly cover all three subcommittee topics, especially transmission
  - Could not review government efforts
  - Inadequate nomenclature to accurately describe different aspects of clinical disease – late Lyme, continuing signs and symptoms after initial antibiotic treatment
    - PTLDS is only a subset of these patients
- Forum to review issues from scientist, clinician and patient viewpoint simultaneously proved valuable

Summary

- *Borrelia burgdorferi* is a formidable pathogen
  - Need to better understand the mechanisms it uses to thwart innate and adaptive immune responses and survive antibiotic exposure
- Human pathophysiology poorly understood
  - Details of host-pathogen interactions need further study
  - How *B. burgdorferi* interacts with specific tissues, especially nervous system is unclear
- Identifying optimum treatment hampered by limited data, lack of biomarkers, previous limitations in trial designs
  - Opportunity to develop patient-centered trials using new tools (patient registries, big data, pragmatic trials to capture what is currently working) to learn about full spectrum of TBD illness
  - Develop nomenclature that is more inclusive and patient-centered, particularly with respect to patients with ongoing symptoms and signs following antibiotic therapy