

Name of Subcommittee:
**Other Tick-borne Diseases
& Co-infections**

Presenters:
Richard Horowitz, Allen Richards

**Tick-Borne Disease
Working Group**

Meeting #4

May 10, 2018

Disclaimer



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

Issues that were addressed by the subcommittee

- **Key Theme 1: Diagnosing Other Tick-Borne Diseases and Co-infections (OTBD&C)**
- **Key Theme 2: Treatment Guidelines for Treating OTBD&C**
- **Key Theme 3: Alpha gal allergy**

- **Other Important Themes: Education, Prevention, Health Care Costs**

Methods



Subcommittee members (11 voting members total)

Members	Type	Stakeholder Group
John Aucott, MD, Working Group Chair, Leadership team	Public	Physician/researcher
Richard Horowitz, MD, Co-Chair	Public	Health care provider
Allen Richards, PhD, Co-Chair	Federal	Scientist (DoD)
Megan Dulaney, MS	Public	Patient
Marna Ericson, PhD	Public	Scientist and family member
Christine Green, MD	Public	Health care provider
Charles Lubelczyk, MPH	Public	Public health
Ulrike Munderloh, DVM, PhD	Public	Scientist
Garth Nicholson, PhD, MD (H)	Public	Scientist
Christopher Paddock, MD, MPHTM	Federal	Pathologist (CDC)
Samuel Perdue, PhD	Federal	Scientist (NIH)
Sam Telford, III, ScD	Public	Scientist
Subcommittee support		
Richard Wolitski, PhD, Designated Federal Officer		
Cat Thomson, Writer		

Meetings and Information Gathering

- Participated in 12 teleconferences, 2 hours each
- Listened to 12 presentations by subject matter experts, including scientists, clinicians, and patient advocates
- Reviewed 200+ journal articles
- Read and considered public comments, patient stories, and clinical case studies

Methods



Development of the Report

- Three writing subgroups
- Agreement obtained through multiple rounds of revision and comments on the report, as well as discussion and fine-tuning of the potential actions during meetings
- Final count: Of 36 Potential Actions voted on by 11 members, all passed:
 - 33 Potential Actions passed unanimously, with 1 abstention and between 1-2 absentee votes per action (scheduled travel & family emergencies arose)
 - 3 Potential Actions were opposed: two by 2 members, and one by another
 - Reasons for opposition include: “New” assays are less of a priority than implementing existing ones or determining their predictive value; The potential action falls outside the scope of the subcommittees charge.

Diagnosing Other Tick-Borne Infections and Co-infections

Diagnosis: Issue #1—Education



- **Gaps in Education of Target Populations**

- **Health care providers** need education about clinical diagnosis, when to order diagnostic tests, and what the results mean.
- **Clinical testing laboratories** need education about selecting appropriate and validated diagnostic assays and what the results mean.
- **Patients, patient family members, and the general public** need education about other tick-borne diseases and coinfections

- **Other Gaps in General Knowledge**

- Studies examining the incidence for concurrent tick-borne infections
- The natural history of untreated tick-borne diseases, issues with persistence, and potential role of coinfections

Diagnosis: Issue #1—Education



- **Opportunities**

- Engaging both traditional and tick-borne disease community provider organizations together to develop best practice guidelines and ensure a comprehensive and balanced approach

- **Threats or challenges**

- Identifying the appropriate agency to do this with respect to authority (national standing; expertise) and capacity to reach all health care providers

Diagnosis: Issue #1—Education



- **Potential Action 1:** Conduct studies to answer important questions about the natural history of other tick-borne diseases and coinfections as well as the human immune response to the infections.
- **Potential Action 2:** Educate health care providers, clinical testing laboratories, patients, and the general public—these could be conducted by a collaborative effort among medical agencies (e.g. HHS), and private medical and patient organizations, as well as knowledgeable clinicians and scientists.
- **Potential Action 3:** Create a tick-borne diseases and coinfections multi-site working group to have a collaborative, standardized approach to data collection and conduct longitudinal cohort natural history studies of sequelae or complications of treated infections.

Diagnosis: Issue #2—Clinical diagnosis



- **Gaps**

- Lack of clinical algorithms and guidance
- A comprehensive list of signs and symptoms, differential diagnoses, and laboratory tests for each infections to confirm or rule out the diagnosis

- **Opportunities**

- Development of new and more inclusive clinical diagnosis algorithms

- **Threats or Challenges**

- Agendas or perceived agendas by different groups and the environment of mistrust that exists between groups impede collaboration and information sharing among them.

- **Potential Action:** Develop flow charts/algorithms for clinical diagnosis of other tick-borne disease and coinfections.

Diagnosis: Issue #3—Laboratory testing



- **Gaps**

- Few diagnostic tests that have undergone interlaboratory comparisons using a defined sample panel developed by an independent agency with well characterized samples of known provenance
- New, more sensitive and specific assays need to be available on site.
- Selecting the right samples for specific infections
 - Skin biopsies and the dermal niche
 - Combinations of methods (serology, PCR, and culture)
 - Advanced imaging techniques for skin and other tissues + new probe technologies
- Animal models
- Timelines for testing

- **Opportunities**

- New technology has the potential improve the direct detection of an infecting agent.
 - Nucleic acid amplification tests (PCR), RNA testing, transcriptome analysis, NGS, chemokine assays, metabolic biosignatures, etc.

Diagnosis: Issue #3—Laboratory testing



• Threats or Challenges

- Possible conflict of interest for those developing new technologies
- Testing often performed using non-FDA approved laboratory developed tests or "in-house" tests performed in a Clinical Laboratory Improvement Amendments (CLIA) approved or non-CLIA approved lab.
- Predictive value of laboratory developed tests is not known unless there is independent evaluation of their predictive value.
- Laboratories' methods may not be fully disclosed, and independent evaluations may affect the economic value of the tests to a company or a patented technologies value to the inventor/researcher.
- Availability of known positive samples: Who should acquire such samples and designate their status?

Diagnosis: Issue #3—Laboratory testing



- **Potential Action 1:** Develop flow charts or algorithms for clinical diagnosis and laboratory testing for acute and chronic illnesses.
- **Potential Action 2:** Promote independent validation of laboratory developed tests utilizing panels of control samples that are assessed blindly.
- **Potential Action 3:** Establish realistic goals for new tests (90% vs 100% S&S)
- **Potential Action 4:** Examine ways to optimize sampling (e.g. skin for *B. burgdorferi*, *Rickettsia* spp., *Bartonella* spp.)
- **Potential Action 5:** Develop new and better tests in both acute and chronic presentations based on the needs identified from systematic review.
- **Potential Action 6:** Expand the number of externally validated assays to provide complete coverage of other tick-borne diseases and coinfections.

Diagnosis: Issue #4—Surveillance



- **Gaps**

- **Need for more and improved systematic surveillance studies for other tick-borne diseases and co-infections**

- **Opportunities**

- Multi-disciplinary work groups at the state level provide an opportunity for data and idea exchange on human, veterinary, and epidemiologic issues.
 - Public, private, university, and NGO partners (such as medical institutions)
 - Opportunity for collaborative projects centering on surveillance or recognition of tick-borne diseases
- **Potential Action 1:** Increase resources available for surveillance including collaborative projects centering on surveillance or recognition of tick-borne diseases at the state level.

Key Theme 2



Treatment Guidelines for Treating Other Tick-Borne Diseases & Co-infections

List of Infections



- **Other Tick-Borne Diseases & Co-infections**

- *Anaplasma, Ehrlichia*
- *Babesia (Babesia microti, Babesia duncani)*
- Other *Borrelia*: Relapsing fever borrelia (hard/soft ticks), *Borrelia sensu lato* spp
- Rickettsia: Rocky Mountain spotted fever (RMSF)
- Deer Tick virus (DTV)/Powassan virus (POWV)
- Bartonella species
- Other pathogens: role of Mycoplasma infections in Lyme disease patients

Anaplasma/Ehrlichia: Treatment HGA, HME, HEE



- **Clinical picture:** HGA: asymptomatic to severe febrile illness. Rarely results in death. Look for fever with low white cell counts, low platelet counts, elevated liver functions (also RMSF, Bourbon/Heartland virus & B. miyamotoi infection)
- Non-specific signs/symptoms (fever, headache, joint/muscle pain, occ G.I./ CNS)
- **Pathology:** increased inflammation; immunosuppression; ↑ susceptibility to secondary/opportunistic infections
- **Evidence for Treatment:** Immediately initiate treatment w/ doxycycline & test (antibody tests (IFA), and DNA tests (PCR) for early infection).
- **Do not delay treatment!** Most patients don't recall a tick bite
- Advanced age, immunosuppression & delays in treatment: ↑ severe clinical outcomes

Anaplasma/Ehrlichia: Treatment



- **Potential Action one:** Educate health care providers on the use of doxycycline
 - Doxycycline is first line treatment for all tick bites w/clinical symptoms suggestive of HGA or other associated TBD's
 - Drug of choice in all age groups: pediatric (under the age of 8), pregnancy (short courses). Rifampin is another choice in pregnancy (clinician judgement)
 - Disseminate this information to HCP's: standardized training modules, brochures, e-prescribing information
- **Potential Action Two:** Dedicate resources to determine mechanisms of immune suppression, pro-inflammatory mechanisms post infection

Babesia: Treatment



- **Clinical picture/Syndromic Surveillance:** Over 100 species. Most common: *B. microti*, *B. duncani* (WA-1) in the US.
- **Potential use of a screening questionnaire:** ? Sudden onset of fatigue, headaches, fevers, day/night sweats, chills, flushing, unexplained cough & SOB
- Untreated individuals may have chronic parasitic infection; Advanced age, immunosuppression, splenectomy: ↑ risk of critical outcomes
- **Treatment:** Atovaquone/Azithromycin: Treatment failures have been reported for *B. microti* babesiosis w/ persistence
- **Risks:** Blood supply, pregnancy, solid organ transplantation, age related pathology (similar to *Anaplasma*). Can ↑ symptoms of Lyme disease

Babesia: Treatment



- **Potential Action One:** Increase resources to improve diagnostics, broaden *Babesia* species testing panels (genetic diversity/multiple *Babesia* spp.).
- **Potential Action Two:** Provide health care education for not only Family practice/Internal medicine doctors, but subspecialists, re: signs/symptoms/risks/laboratory evaluation/treatment challenges of Babesiosis.
- **Potential Action Three:** Conduct laboratory research & clinical trials to evaluate new treatment regimens for Babesiosis. Resistance to standard regimens has been reported (medications/alternative medicine protocols) → ↑ morbidity & mortality.
- **Potential Action Four:** Conduct research on immunotherapy/human monoclonal antibodies to control parasitemia while on drug treatment.

Other Borrelia Species: Treatment



- **Species:** *B. miyamotoi* & other Relapsing Fever borrelia, *B. burgdorferi sensu lato* spp.
- Frequency is increasing, and can result in “Lyme-like syndromes” (antibody testing for LD insensitive; will not pick it up)
- **Clinical Picture/Syndromic Surveillance:** Soft ticks (symptoms last 2-9 days & relapse; broad range of symptoms); Hard ticks (BMD): also Lyme-like syndromes
- **Treatment:** TBRF (*B. hermsii*): most drugs work (doxycycline, azithromycin...)
- *Borrelia miyamotoi*: resistant to Amoxicillin (in vitro)
- **Other Risks:** Blood supply, pregnancy (similar to LD, babesiosis, bartonellosis..)

Other Borrelia Species: Treatment



- **Gaps:** Incidence of *Borrelia miyamotoi* disease? Role in other diseases w/ a chronic fatiguing/musculoskeletal component (Chronic Fatigue Syndrome, Fibromyalgia)?
- **Challenges:** Persistence (Bm, Sensu lato spp.) post treatment w/standard AB's
- **Potential Action One:** Improve public education on prevention tick bites, and educate health care providers on the signs/symptoms/transmission RF borrelia
- **Potential Action Two:** Diagnostics: expand routine testing panels (5% of the US population suffers from Chronic Fatigue Syndrome/Fibromyalgia)
- **Potential Action Three:** Treatment: Evaluate efficacy of treatment regimens against relapsing fever borrelia transmitted by hard/soft ticks, especially when different co-infections are present, as persistent infection has been reported

Deer Tick Virus/Powassan virus: Treatment



- **Clinical Picture:** May result in asymptomatic infection. 50% of survivors with neurological symptoms have severe permanent neurological symptoms (recurrent headaches, weakness, memory problems). 10% of infections are fatal
- **Increased Risk:** + serology for POWV in TBD samples was 9.4% in regions where Lyme is endemic (Thomm et al., 2018)
- **Gaps:** ? Transmitted from raw milk (TBEV), ? Persistent infection ? Birth defects
- **Treatment:** Supportive. No effective treatment exists for severe disease, with a 10-15% mortality rate. High dose steroids or IVIG may be helpful?
- **Potential Action One:** ↑ resources for research into effective treatment
- **Potential Action Two:** Conduct research (animal models) re: modes of transmission & whether persistence exists after an acute infection (Zika, WNV)



Rickettsia (Rocky Mountain Spotted Fever): Treatment

- **Increased Risk:** 15% of all reported fatalities of RMSF are children under 10 yo; Transmission via blood transfusion has also been described.
- **Clinical Picture:** Difficult to diagnose in early stages due to non specific symptoms (fevers, headache, nausea, vomiting, muscle pain, abd pain, rash...)
- **Severe disease:** Cardiac, respiratory symptoms, renal failure, seizure, coma.. Long term sequelae: hearing loss, bladder/bowel prob's, learning disabilities...
- **Treatment:** Treat presumptively & immediately w/ doxycycline on clinical & epidemiological findings. Don't wait for a + test, don't stop treating w/ neg test
- **Potential Action One:** Educate health care providers on non-specific signs/symptoms. Use doxycycline as 1st line therapy in children/pregnancy.
- **Potential Action Two:** Treat RMSF presumptively; never delay/stop treatment.

Bartonella: Treatment



- **Challenges: multiple species:** Difficult to detect by standard testing; stealth pathogens that evade the immune system & ↑ symptomatology seen w/ Lyme dx; manipulate the immune system; persist and often relapse post treatment
- **Clinical Picture:** Benign to severe/life threatening disease. Can affect every organ & tissue in the body → G.I., cardiovascular, rheumatologic, neuropsychiatric
- **Vectors:** Fleas, *Ixodes ricinus* ticks, biting flies, lice, potentially spiders, mites..
- **Treatment:** At least 2 antibiotics (i.e., doxycycline & rifampin..), failures possible
- **Gaps:** Mode of transmission, establishing proof of infection, treating effectively

Bartonella: Treatment



- **Potential Action One:** Improve & expand diagnostic assays, ↑ range of species
Explore how multiple pathogens interact (Lyme, *Bartonella*): ? Effect on immunity
- **Potential Action Two:** Conduct trials to evaluate more effective treatments.
Failures/clinical relapses post antibiotic therapy have been reported
- **Potential Action Three:** Allocate resources to improve and expand research into the interaction between simultaneous infecting pathogens and the effect on the immune response of two or more pathogens.
- **Potential Action Four:** Conduct animal and human clinical trials to evaluate more effective treatment protocols, as *Bartonella* has been shown to persist despite single or combination therapy.
- **Potential Action Five:** Allocate resources to conduct research to determine the risk of transmitting multiple tick-borne pathogens via the blood supply.

Role of Other Pathogens: Mycoplasma

Role of Other Sources of Inflammation



- **Challenges: multiple species:** *Mycoplasma* are difficult to detect by standard testing; manipulate the immune system; persist and can relapse post treatment
- Approximately 70% of chronic LD patients have systemic *Mycoplasma* infections
- **Gaps:** ? Transmission by ticks; problems with establishing proof of infection (multiple species, intracellular). Do *Mycoplasma* increase symptoms in PTLDS? How can we effectively treat? (persistence is possible with single drug regimens)
- **Potential Action One:** Review the role of overlapping causes of inflammation in LD patients, such as *Mycoplasma* infections and environmental toxins. These have both been associated with autoimmune phenomenon.
- **Potential Action Two:** Conduct research on the role of free radical oxidative stress and cytokine production during tick-borne infection. Downstream effects of inflammation may result in disabling symptoms. Allocate resources to conduct clinical trials to identify contributing causes and confounding factors.

Alpha-gal Meat Allergy

Alpha Gal Meat Allergy



- **Background:** The bite(s) of a lone star tick (and other ticks) can result in an allergic reaction, leading to an anaphylactic reaction which can be life threatening. The reaction can be delayed (minutes to hours)
- Alpha gal meat allergy is spreading, as is the range of the lone star tick in U.S.
- **Gaps:** Lack of surveillance (true numbers of individuals affected are unknown)
- Education and awareness is needed (preventing tick bites, range of potential triggers, i.e., the role of other triggers such as personal care/medical products/nutritional products needs further investigation)
- **Possible Action One:** Increase education and awareness pre-diagnosis, and counseling after diagnosis. Labelling on food may be inadequate
- **Possible Action Two:** Dedicate additional resources to vector control
- **Possible Action Three:** Increase funding for immunologic and animal model research to identify and better understand the tick proteins that cause alpha-gal meat allergy.

Discussion: Challenges & Limitations



- **Staff support** was great
- **The time frame** was challenging
 - Not enough time to hear all the speakers while simultaneously writing and editing the document
 - Not enough time for editing
 - There were several issues on diagnostics and treatment that members wanted to keep discussing
- **Were the data you obtained complete and what you needed?** Yes
- **Are there any sections of the report that you have concerns about re: the info provided?** No

Discussion: Big Picture Summary: Why OTBD's & Co-infections Are Important



- Co-infections in ticks are widespread w/ multiple pathogens & some are transmitted rapidly after a tick bite. Some tick-borne disorders (like alpha gal allergy), anaplasmosis, RMSF and POWV can be fatal
- These infections are not only transmitted by ticks, but some are also present in the blood supply (increasing the risk of transfusion), & can be passed on to pregnant women and fetuses, ↑ morbidity/mortality
- Inadequate diagnostic and treatment protocols for other tick-borne infections and co-infections are potentially ↑ symptoms in Lyme disease & PTLDS, contributing to increasing health care costs and disability