THE CONNECTION BETWEEN MENTAL HEALTH AND THE MAJOR TICK-BORNE DISEASES

CLINICAL AND LABORATORY DIAGNOSIS

Joseph J. Burrascano Jr. M.D.

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Implicated in mental illness

Infections

- TBDs: Borrelia, Bartonella, Babesia, Rickettsia family- *our focus today*
- Systemic: Strep, Mycoplasma, Chlamydiae, Brucella, Coxsiella, etc.
- Treponemes, Leptospira
- Parasites: Toxoplasma, Malaria, worms
- Fungi: Candida, Aspergillus, Cryptococcus
- Viruses: Many, both common and rare

Non-infectious causes

- Systemic inflammation
- Toxins: metals, organic chemicals, mycotoxins
- Previous significant stressors (PTSD, ACH, etc.)

Lyme: How do we define *NEUROBORRELIOSIS?*

Literature definition requires demonstration of intrathecal production of antibody

HOWEVER:

- CSF antibody positivity occurs in only 9% of cases of Lyme meningitis (P. Coyle, neurologist, SUNY Stony Brook)
- Bb disseminate immediately after reaching the blood stream and can appear within the CNS within hours to days so virtually ALL Lyme, even early Lyme, can involve the CNS

CONCLUSIONS:

- ALL Lyme infections potentially involve the CNS even if the spinal fluid tests negative
- It is inappropriate to deny neuroborreliosis simply on the basis of a negative CSF antibody

How do we define neuropathy?

- Unmyelinated nerve fibers mediate autonomic functions and temperature, burning pain and itch
- Myelinated fibers transmit signals faster and mediate most motor and sensory functions including vision and hearing
- Both fibers are present in the central nervous system
- Methods that measure nerve function like electromyography and nerve conduction miss up to half the cases of demyelination
- Functional tests of autonomic testing such as sweating response are similarly insensitive

HOWEVER, neuropathy is COMMON in Lyme

Demonstrating neuropathy microscopically

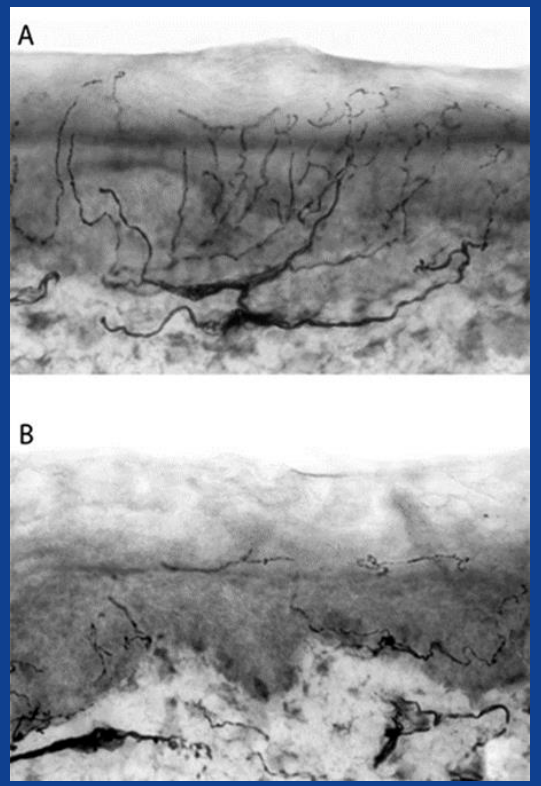
Courtesy of B. Mozayeni, M. Ericson, and A. Katz

Unmyelinated fibers

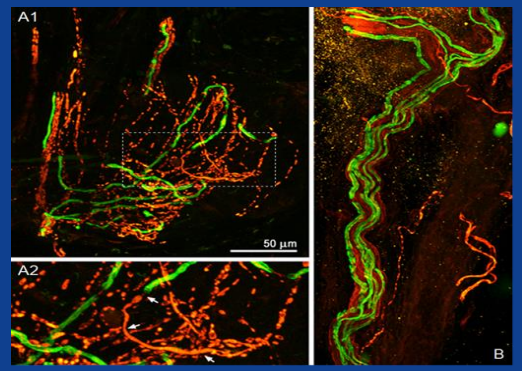
Normal biopsy

Lyme patient

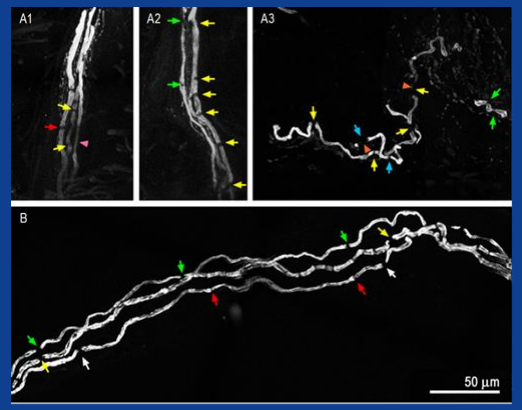
Note markedly decreased fiber count



Myelinated fibers



Staining axons and myelin, visualized with confocal microscopy



Using this technique to measure intermodal length and intermodal gap

“Lyme” is usually more than just Borrelia

Study: 10,000+ patient samples

- 37.3% were positive for Babesia species
- 32.1% for Lyme Borrelia
- 27.7% for TBRF Borrelia
- 19.1% for Bartonella
- 16.7% for Anaplasma
- 12.8% for Rickettsia
- 6.9% for Ehrlichia

Co-infections

- 40% tested positive for two pathogens
- 15% tested positive for three pathogens
- 4.6% tested positive for four pathogens
- 0.7% tested positive for five pathogens

Clinical Lyme disease: Borrelia in the USA

Lyme disease: Bb sl (B. Burgdorferi *senso lato)*

B. burgdorferi B31 (Bb ss)

B. burgdorferi 297

B. californiensis

B. mayonii

B. afzelii

B. garinii

B. spielmanii

B. valaisiana

Tick-borne relapsing fever Borrelia (TBRF)

B. hermsii

B. miyamotoi

B. turcica

B. turicatae

B. coriaceae

B. parkeri

B. texasensis

- Species in red are the only ones that the large commercial labs will test
- But the rest may also infect USA patients, and must be included
- IGeneX offers testing that can detect all these species

Tick-borne relapsing fever mimics Lyme

90 patients who met the published clinical case definition of CHRONIC LYME DISEASE (*not suspected to have TBRF*)

- 46 positive for Bb s.l.
  - Bb s.s., B. californiensis, B. spielmanii, B. afzelii, B. garinii plus other Bb s.l. species that could not be identified
- 56 positive for TBRF- more than half!!!
  - B. hermsii, B. miyamotoi, B. turicatae, B. turcica, plus other TBRF species that could not be identified
- 8 positive for both Bb s.l. and TBRF

CONCLUSION: When testing for Lyme, testing for TBRF MUST be included

Lyme Disease: Diversity of Borrelia Species in California and Mexico Detected Using a Novel Immunoblot Assay. Fesler, MC et. Al. Healthcare 2020, 8,97; doi:10.3390/healthcare8020097

Borreliosis: Key clinical features

- Multisystem-
  - Typically includes musculoskeletal, neurologic and general symptoms, with subtle cardiac involvement
- Migratory- symptoms move around
  - Is the only illness with migratory neuropathy
  - Joint involvement also can migrate
- Cyclic-
  - Classic 4-week cycle with Lyme Borrelia
  - Cycles may be shorter with TBRF

These are reasons why many Lyme patients are thought to be malingering

- *Very helpful to have patients keep a symptom diary and calendar*
- Record symptoms and patterns and also temperature record-
  - Low in AM, higher in afternoon (typically 99-100)

Physical exam

Subtle signs are always present- but you have to look!

- Appearance, cognition and speech
- Rashes, skin temperature and color
- Orthostatic hypotension- and observe change in pulse
- Neuro- cranial nerves incl. gag and corneal reflexes, EOMs, DTRs- absent/decreased, delayed relaxation, brisk, clonus
- Joints- synovial thickening, tenderness, heat, redness, effusions, ROM
- Muscles and tendons- nodules, tenderness, weakness
- Nuchal rigidity; “Lyme shrug”: meningeal irritation
- Hepatosplenomegaly, lymphadenopathy

Don’t forget that you are also looking for other possible diagnoses!

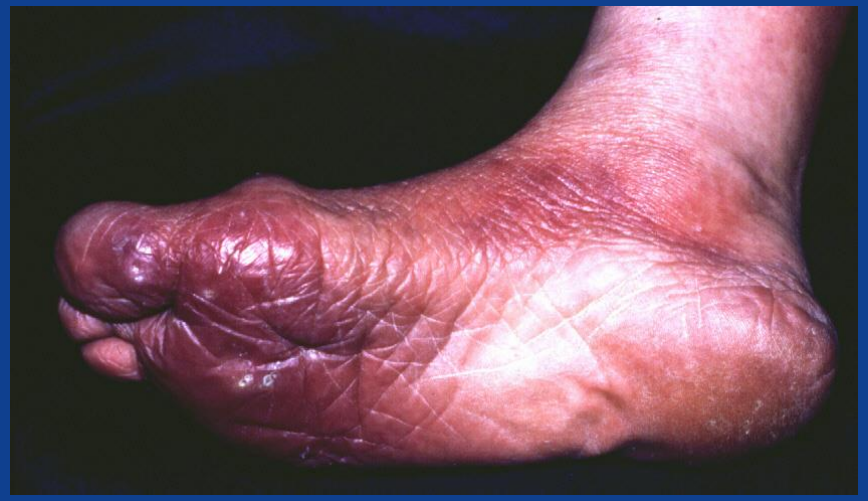
Acrodermatitis Chronica Atrophicans (ACA)

Appears late in the illness

- Usually associated with *B. afzelii* but some cases associated with *B. garinii* have been reported
- Inflamed skin slowly evolves into thinned, atrophic skin and sclerotic patches are possible
- Underlying neuropathy

Associated with neuroborreliosis!

- Skin biopsy may be useful



Laboratory testing for Lyme- indirect tests

- "Standard" serologies- IFA, ELISA and Western Blot
  - Insensitive (~50%), limited specificity (70+%), minimal species coverage
  - Trade-off between sensitivity and specificity
- ImmunoBlot
  - **Vastly better**- more sensitive (90+%), more specific (97+%), and able to detect a broad range of species and strains
  - Can be done on CSF
- T-cell response assay ("IGXSpot")
  - Good in early Lyme but not as sensitive as the ImmunoBlot; helpful in some late, chronic cases and when there is B-cell dysfunction

OK to do indirect tests while on treatment

Validation of the Lyme ImmunoBlot

GAME CHANGER!

- IGeneX Lyme ImmunoBlot picked up 93% of <u>early</u> cases!!
- No other test *of any kind* has been demonstrated to do this
- Late-appearing IgM is significant- note the 99% specificity
- Often seen in advanced disease

Patients with:	n	2-tier Serological Testing for LD (ELISA follwed by Western blots)			Lyme ImmunoBlots		
		IgM	IgG	G+M	IgM	IgG	G+M
Early Lyme Acute (Stage 1)	15	20.0%	0.0%	20.0%	66.7%	46.7%	93.3%
Early Lyme Convalescent (Stage 1)	15	66.7%	33.3%	80.0%	86.7%	46.7%	100.0%
Neurological Lyme (Stage 2)	9	100.0%	55.6%	100.0%	100.0%	77.8%	100.0%
Lyme arthitis (Stage 3)	10	10.0%	100.0%	100.0%	30.0%	100.0%	100.0%
Total	49	46.9%	40.8%	69.4%	71.4%	63.3%	98.0%

Samples	Negatives	Lyme ImmunoBlots					
		Lyme IB In-house criteria			Lyme IB CDC criteria		
		IgM	IgG	M+G	IgM	IgG	M+G
CDC set 1	5	0	0	0	0	0	0
CDC set 2	20	0	1	1	0	0	0
PT samples	11	0	0	0	0	0	0
Autoimmune	42	0	0	0	0	0	0
Viral infections	46	1	1	2	0	0	0
RPR +	28	0	2	2	0	1	1
Specificity %		**99.3**	**97.4**	**96.7**	**100**	**99.3**	**99.3**

TBRF ImmunoBlot (IGeneX)

Standard tests are either the inaccurate IFA for B. hermsii only, or a single antigen ELISA for B. miyamotoi. *Standard testing is not available for any of the other TBRF species*

In contrast, the TBRF ImmunoBlot:

- Able to detect the most commonly found TBRF species, not just B. hermsii or B. miyamotoi
- Significantly increased sensitivity (>97%)
- Significantly increased specificity (>99%)
- Species-specific- no cross reactivity between TBRF and Lyme Borrelia

Laboratory testing for Lyme- direct tests

- Standard PCR
  - Extremely insensitive in blood (<10%); somewhat useful for tissue biopsies
- Culture (cePCR- IGeneX)
  - Potentially 10-100 X more sensitive than PCR
  - Genus-level detection ensures capture of a broad array of strains and species
  - Can be done on the CSF

The above direct tests should NOT be done within 4 weeks of last treatment

- Urine antigen capture (CSF too)
  - Great when blood draws are impractical or impossible
  - Best results if done during symptom flares and Herxheimer reactions even if on treatment
  - Lyme only- not TBRF

Culturing blood for TBD pathogens

CULTURING IS THE GOLD STANDARD

IGeneX cePCR- “Culture-enhanced PCR”

- Available for Lyme, TBRF, Bartonella, Babesia, Ehrlichia, Anaplasma and the Rickettsias
- Genus level reporting-
  - Broadens number of pathogens being detected (but will not identify species)
- Specificity >99%
- Sensitivity 10-100X standard PCR

Each type of pathogen requires a different culture medium, so tests must be ordered individually

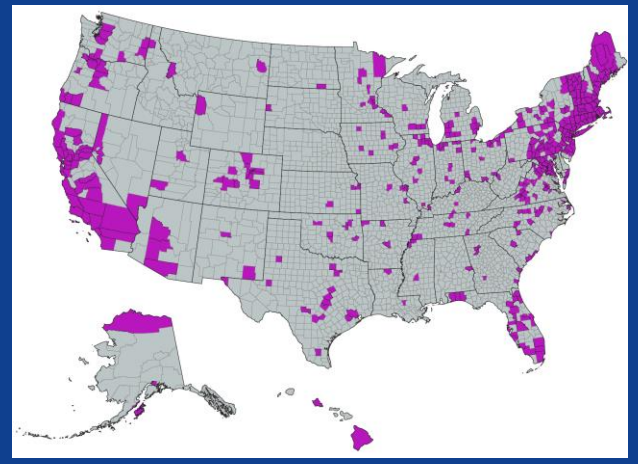
Testing recommendations- Borrelia

- Use tests that can detect the broadest range of species
  - Lyme- Bb sl-
    - ImmunoBlot and culture are preferred and can be done on the CSF
    - Urine antigen capture, T-cell response assay in certain cases
  - TBRF-
    - ImmunoBlot and culture
- Combine multiple testing methods to maximize yield
  - ImmunoBlots + Culture (cePCR): indirect + direct tests
  - Option to add urine antigen testing and T-cell response
  - Synovial biopsy with PCR testing has a reasonably good yield

BARTONELLA-
Documented in at least 49 states

Extremely common in Lyme/TBD patients

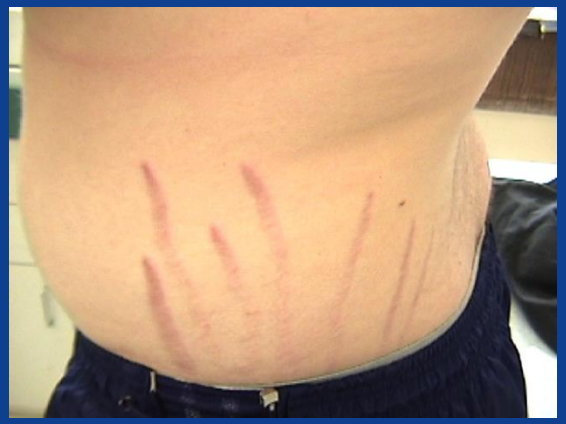
- Is easily confused with Lyme
- Over 45 species known to exist!!
- Many ways to acquire an infection:
  - Common vectors: fleas, mosquitos, biting flies, mites, red ants
  - Now demonstrated that ticks may also transmit Bartonella
  - Animal bites and scratches, needle sticks, maternal-fetal
- Worldwide distribution- even found far above the arctic circle!

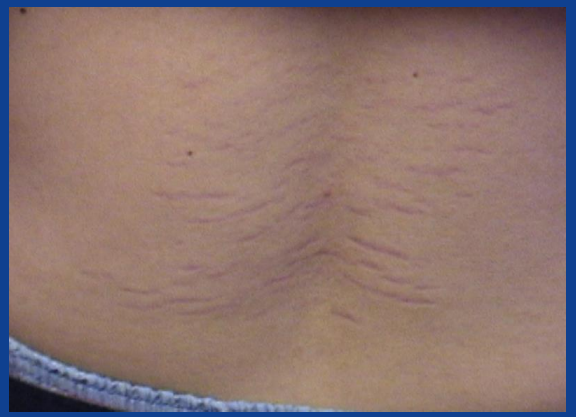


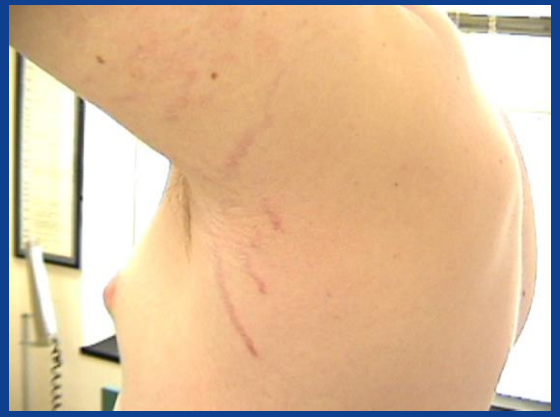
Bartonella- unique clinical features

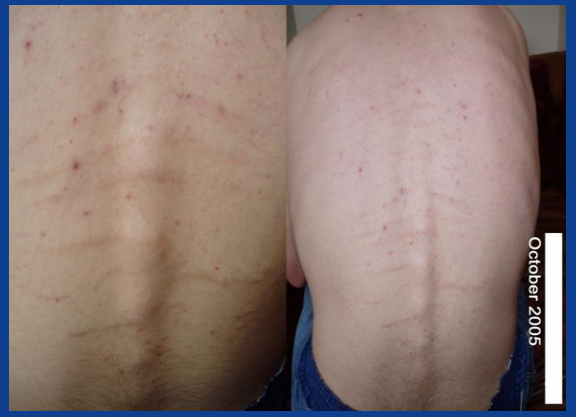
- CNS- irritability and global dysfunction
  - Anxiety, panic attacks, antisocial behavior, rage attacks, insomnia, depression, tremors, seizures, ataxia, hallucinations, schizophrenia, dementia
- Eyes- uveitis, retinitis, retinal artery and vein thromboses
- Regional lymphadenopathy
- Connective tissues- tender nodules (skin, along fascia), sore soles, tendonitis, bone pain, painful joints without synovial swelling
- Peculiar skin manifestations:
  - “Bartonella tracks” (also referred to as BACL- Bartonella Associated Cutaneous Lesions)
  - “Bacilliary angiomatosis” (red bumps that may scab)
- GI involvement
  - Gastritis, mesenteric lymphadenitis, peliosis hepatis

Bartonella rashes

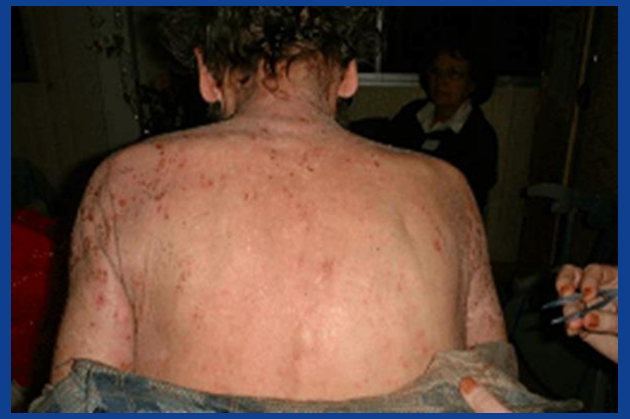


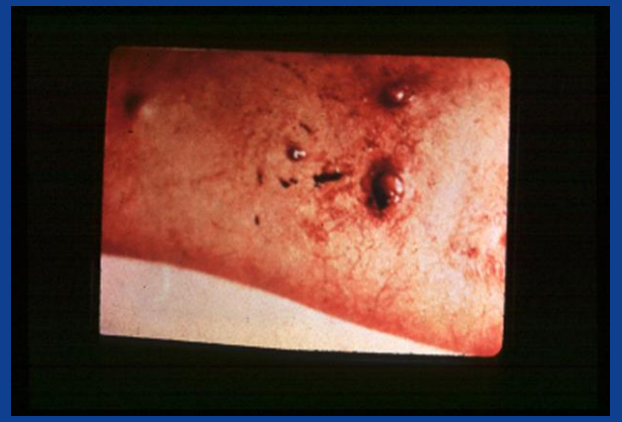






BARTONELLA TRACKS/BACL





BACILIARY ANGIOMATOSIS

Bartonella tests

- IFA- old technology; designed to detect only B. henselae.
- ImmunoBlot- More sensitive, more specific, and able to detect multiple species- Has replaced the IFA
- Standard PCR- Detects presence of DNA of the organism after amplification; however, limited sensitivity (only 6%!!)
- Culture (cePCR)- increases sensitivity (by at least a factor of 10) and overcomes many of the technical limitations of standard PCRs; genus-level detection allows for broad coverage
- FISH- (Fluorescent in-situ hybridization)- Direct visualization via fluorescent RNA probe; is genus-specific thus offers extended species coverage; able to detect organisms in biofilms

Bartonella testing- Recommendations

Notoriously difficult to detect!

- Because of stealth features, no single test is 100% sensitive
- Also, multiple species are infecting our patients
- Therefore need highest sensitivity and broadest species coverage

RECOMMENDATION: Test by multiple methods

- ImmunoBlot + FISH + Culture (cePCR)
- If there is a known B-cell functional defect, add the T-cell IGXSpot assay

BABESIOSIS

Malaria-like intra-erythrocytic parasite

- Is the most common co-infection in Lyme patients

Unique clinical features:

- Causes fever, sweats, migraine-like headache, air hunger, cough, profound fatigue, balance issues and cognitive dysfunction
- Many other symptoms overlap with Lyme and TBRF
- Transmitted by the same tick that transmits Lyme
- The two dominant USA species are B. microti and B. duncani
- B. MO-1, B. odocoilei, B. divergens- also occasionally seen
- Rarely, atypical species can also be found in humans

Babesia testing

- IFA- Insensitive and outdated; need separate IFAs for B. microti and for B. duncani; not available for other species
- Immunoblot- Far more sensitive than the IFA and offers broad species coverage
- Stained blood smear- Done in hospitals- only useful within first week of infection
- FISH- direct detection of Babesia RNA on a blood smear
  - Far more sensitive than standard smear (>100X); can detect organisms in biofilms; genus-level test so has broad coverage
- Culture (cePCR)- is a genus-level test so it can detect microti, duncani and others

Babesia testing- Recommendations

Notoriously difficult to detect!

- Because of complex parasite biology, no single test is 100% sensitive
- Also, now finding atypical species previously not expected
- Therefore need highest sensitivity and broadest species coverage

Testing by multiple methods is recommended

- ImmunoBlot + FISH + Culture (cePCR)
- If there is a known B-cell functional defect, add the T-cell IGXSpot assay

Rickettsia family

Labs are seeing an increase in incidence of all the Rickettsias!

Anaplasma, Ehrlichia and Rocky Mountain Spotted Fever

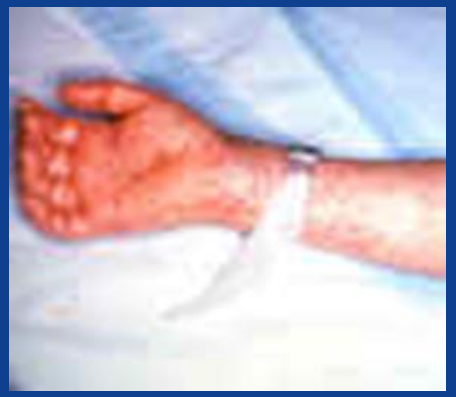
- *CAN BE FATAL!!*

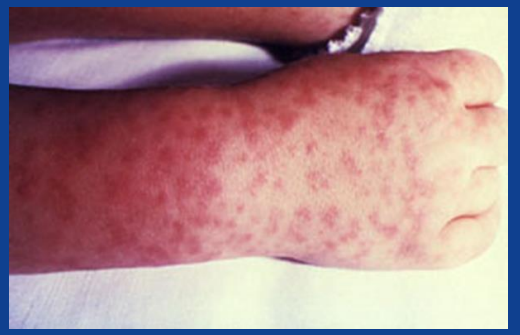
CLINICAL:

- Acute fever, knife-like headache, myalgias, malaise
- Acutely, often associated with low WBCs, low platelets, and elevated LFTs
- RMSF rash- vasculitic; blanches with pressure and refills from center; includes palms and soles; Rash occasionally seen in the others (<5%)

Chronic infections are increasingly being seen!

- Clue: ongoing leucopenia, thrombocytopenia, elevated LFTs





Rickettsia family- Testing

Ehrlichia and Anaplasma

- Serology (IFA)
- Culture (cePCR)- replaces standard PCR

RMSF

- Serology (IFA)
- Standard PCR (culturing not allowed unless lab is certified for Biosafety Level 4)

Best advice is to use all available methods when testing for these

Tips to optimize TBD testing

- Timing
  - Do direct tests (cePCR, FISH) when pathogenemia is highest
    - Early disease, disease flares, immune compromised
    - Do NOT do direct tests if currently on treatment
  - Do indirect tests (ImmunoBlots, IGXSpot T-cell test) when immune response is highest
    - Disseminated but not chronic illness, intact immunity
    - OK to do while on treatment
- Combine methods to maximize sensitivity
  - Direct test + indirect test
  - EXAMPLE: cePCR + Immunoblots

TBD INFECTION CLINICAL GUIDE

INFECTION	ONSET	CYCLES	SYMPTOMS	HEADACHE	FEVER	SWEATS	RELAPSE
LYME	Gradual	4 weeks	Multisystem Migratory, cyclic Joints	Nuchal “Lyme shrug”	Afternoon	No	Slow (weeks)
BARTONELLA	Gradual	No	Excitatory Soft tissues Lymphadenopathy	No	Morning	Light	Rapid (days)
BABESIA	Can be abrupt	5-7 days	Tippy, air hunger/cough Worsens everything	Band-like, Migraine-like	Any time	Drenching	Slow (weeks)
RICKETTSIAS	Abrupt	No	Acute flu Muscles	Knife in the eyes	Constant	Acutely	Gradual

TBD TESTING GUIDE

TEST	METHOD	FEATURES	WHEN TO USE	ACCURACY
IFA, ELISA, WB	Serology	Single species	Not recommended	False negatives False positives
ImmunoBlot	Serology	Recombinant Ag's Multiple species	All stages	Maximal
T-cell response assay	Mitogen stimulation assay	Limited time window	Early and In B-cell dysfunction	Medium- depends on timing
PCR	DNA detection	Fluids and tissues	Tissues only if possible	Insensitive but very specific
Culture (cePCR)	Culture with pathogen ID confirmed by PCR	Blood only	All stages but not if on treatment	Maximal
FISH	RNA-stained blood slide	The best test if biofilms are present	All stages but not if on treatment	Good
Urine antigen capture	Direct antigen detection	Lyme only	When blood draws are to be avoided	Good

Testing for non-infectious factors

Inflammation

- Cytokine panels
- Antineuronal antibodies (Cunningham panel)
- CBC with differential count, ESR, HS-CRP, Procalcitonin, VEGF, ANA, RF

Toxins

- Toxic metals- manganese, lead, mercury, aluminum
- Mycotoxins
- Environmental- insecticides, glyphosate, other organic chemicals

CONCLUSIONS

- Tick-borne diseases are a major factor in cognitive and neurological dysfunction and in many types of mental illnesses
- Represent a potential treatable cause so the diagnosis MUST NOT BE MISSED!
- It is up to the clinician to be aware of this and use the most sensitive, most comprehensive testing methods available
- Do not make the mistake of limiting testing by not considering all likely pathogens and by using tests of limited scope
- Take advantage of the many resources now available to help you in this task


Thank you!
Q&A to follow