IGeneX Inc.

BEYOND BALANCE INC.®

# TICK-BORNE INFECTIONS: CLINICAL DIAGNOSIS AND BOTANICAL MANAGEMENT

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Any information contained herein is solely for consideration by a trained medical practitioner and not a recommendation for treatment.

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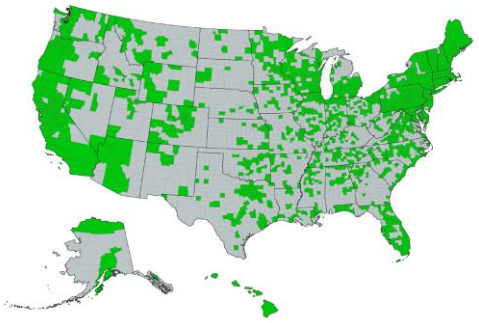
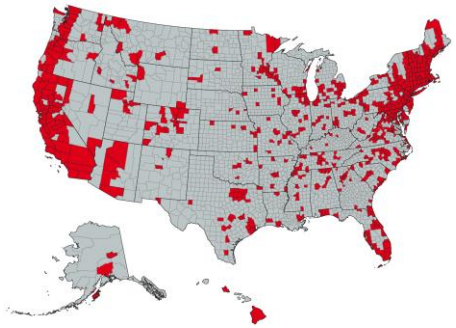
# IT'S MORE THAN LYME DISEASE

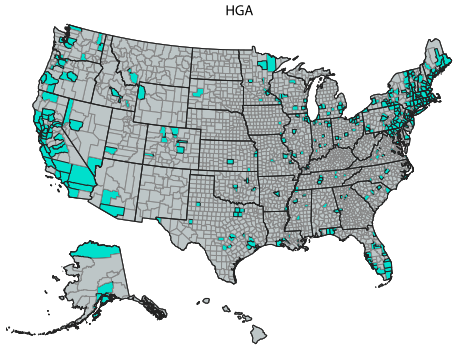
Lyme disease



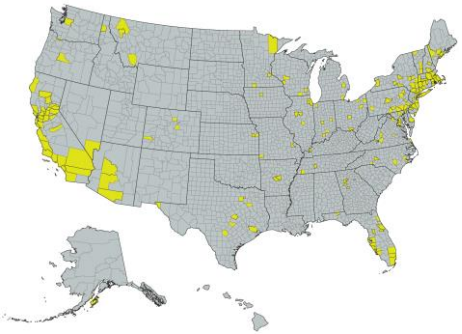
Babesia



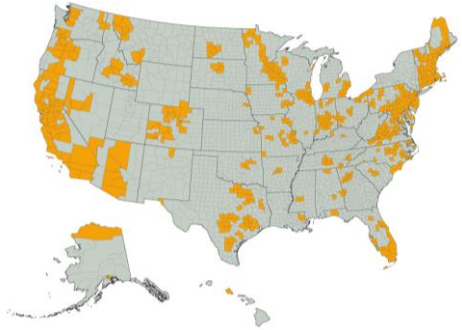
Anaplasma



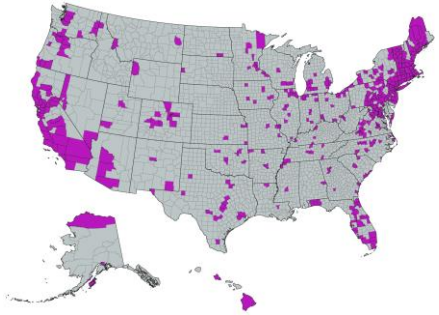

Rickettsia



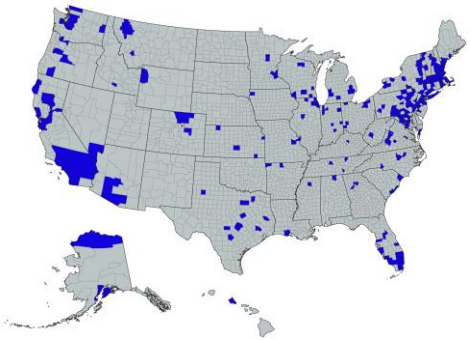
TBRF



Bartonella



Ehrlichia



Opportunists

# DIVERSITY OF TICK-BORNE PATHOGENS

**A 2018 study of 10,000+ patient samples tested at IGeneX**

- 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

# BORRELIA SPECIES IN USA

**B. Burgdorferi *senso lato* (Lyme)**

*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 IFA, ELISA, and Western Blot tests have been validated to detect
- But the rest are also infecting USA patients and are included with IGeneX testing

# LYME DISEASE - CARDINAL CLINICAL FEATURES

## MULTISYSTEM

- Joints, peripheral nervous system, central nervous system
- Skin, cardiac, GI and others possible
- MANY nonspecific symptoms – fatigue, headache, cognitive difficulties, malaise

## MIGRATORY

- Symptom location and organ type will vary
- The only infection known to cause migratory neuropathy and migratory arthritis

## CYCLIC

- Classic 4-week cycle of symptoms in Lyme; may be shorter cycle in TBRF

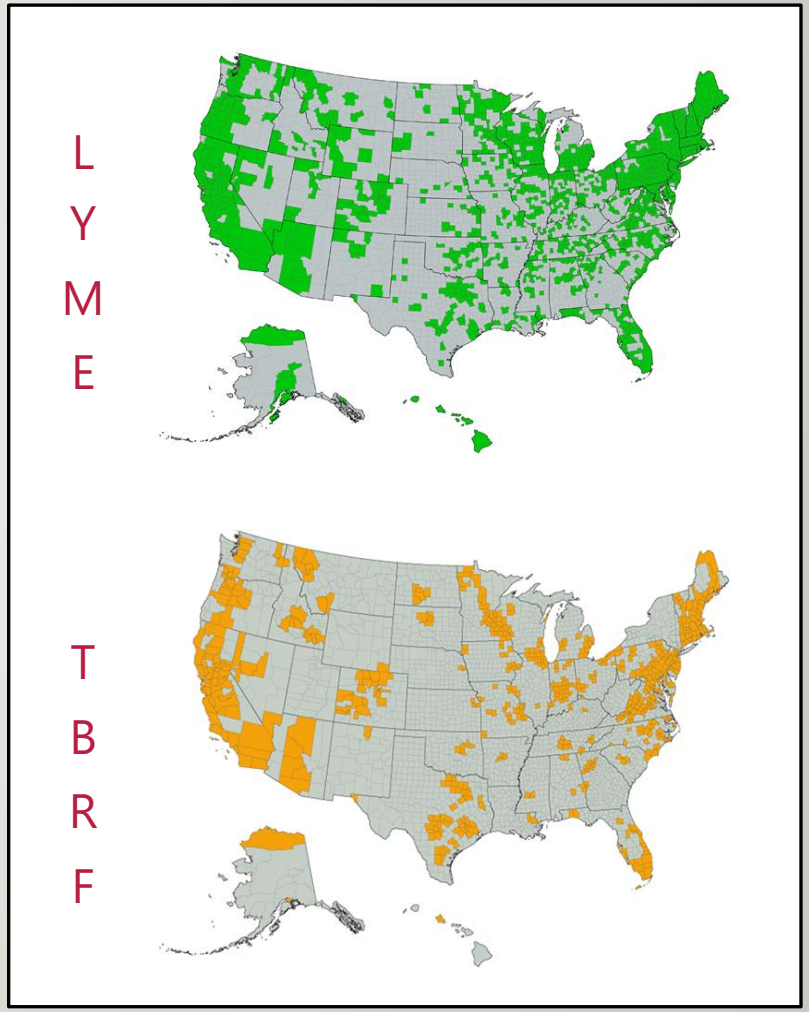
# TICK-BORNE RELAPSING FEVER (TBRF) - *UNEXPECTED CLINICAL PRESENTATION!*

## Classic Description of TBRF

- Acute illness - high fever and severe malaise, lasting for just a few days, ending with severe sweats and weakness, followed by several days of relative wellness
- Then the acute symptoms recur and repeat every 5 to 7 days

## TBRF Mimicking Lyme

- In a large number of patients, TBRF will clinically present as Lyme disease and they get tested for Lyme, and not TBRF



# TBRF MIMICKING LYME

**Is surprisingly common!**

543 US patients with suspected Lyme:

- 32% were positive for Antibodies to Lyme Borrelia
- 22% were positive for Ab to Relapsing Fever Borrelia
- 7% were positive for Ab to **both** LB and RFB

- Clinically, they ALL resembled Lyme patients, not “relapsing fever” patients

**CONCLUSION: Lyme testing must also include TBRF**

# CAN THIS BE "SERONEGATIVE LYME"?

*Seronegativity may simply be due to testing for the wrong species!*

- **NONE** of the commercial or test-kit Lyme IFAs, ELISAs, western blots, PCRs or T-cell tests have been validated for all the Lyme Borrelia (Bb sl), or for *any* TBRF
- Similarly, commercial TBRF serologic testing has only been validated against two species (hermsii and miyamotoi) and each test has to be ordered individually

## Solutions

- Always test for both Lyme and TBRF for initial diagnosis and for re-evaluations
- For serologies, use ImmunoBlots as they are inclusive of multiple species
- For direct testing, use the Culture (cePCR) as it offers genus-level detection

# LABORATORY TESTING FOR BORRELIA

- IFA and ELISA - notoriously insensitive (may be less than 50%!!) and false positives commonly occur (viral infections, autoimmunity, other spirochetes); single species. NOT RECOMMENDED
- Western Blot - also insensitive (50%-70%); false positives also possible; single species (usually the lab strain B31)
- ImmunoBlot (IGeneX) - Far greater sensitivity (93%-99%), far greater specificity (97%-100%) and MULTISPECIES capable
- T-cell stimulation assay (IGXSpot - IGeneX) - genus-level detection of T-cell reactivity; positive reflects past infection - MULTISPECIES
- Culture (cePCR - IGeneX) - Far greater sensitivity than PCR; specificity 100%; MULTISPECIES

# LYME IMMUNOBLOT

Recombinant technology makes the ImmunoBlot more sensitive and more specific than other serologies

- Sensitivity
  - Able to detect IgM and even IgG IN EARLY LYME, with a combined sensitivity of 93%
  - In Established cases, sensitivity demonstrated to be 90%-100%
- Specificity - 97% -100% in validation studies with unknowns
  - A positive IgM, EVEN IN LATE DISEASE, is 97% specific- can no longer dismiss this
- Multispecies capability
  - In Lyme, can detect all Bb sl
- Basically, if free antibody is present, you will get a positive result

# TBRF IMMUNOBLOT PERFORMANCE

| TBRF ImmunoBlot: Sensitivity Study Summary<br>15 PCR + Patients- 7 patients: 2 samples/patient; 1 patient: 1 sample | | | | | | |
|---|---|---|---|---|---|---|
| Sample Type | Number | IgM (+) | IgG (+) | IgM & IgG (+) | Total (+) | **Sensitivity** |
| 1st Sample (acute) | 15 | 7 | 1 | 2 | 10 | **66.7%** |
| 2nd Sample (convalescent | 7 | 4 | 1 | 2 | 7 | **100%** |

- Sensitivity 100% in late infections; 67% in early disease
- Specificity 98%
- Able to detect all major pathogenic species known to affect USA patients

| **Sample Types** | N | **IgM (+)** | **IgG (+)** | **IgM or IgG (+)** |
|---|---|---|---|---|
| Endemic area control | 10 | 0 | 0 | |
| Fibromyalgia | 5 | 0 | 0 | |
| Mononucleosis | 9 | 0 | 0 | |
| Multiple sclerosis | 5 | 1 | 0 | 1 |
| Non-endemic area control | 14 | 0 | 0 | |
| Periodontitis | 5 | 0 | 0 | |
| Rheumatoid arthritis | 14 | 0 | 0 | |
| Syphilis | 13 | 1 | 2 | 2 |
| HIV-1 infection | 4 | 0 | 0 | |
| Cytomegalovirus infection | 5 | 0 | 1 | 1 |
| Autoimmune and Allergy | 33 | 1 | 0 | 1 |
| *Borrelia burgdorferi* infection | 12 | 0 | 0 | |
| *Bartonella henselae* infection | 7 | 0 | 0 | |
| Human granulocytic anaplasmosis | 16 | 0 | 0 | |
| *Babesia microti* infection | 14 | 0 | 0 | |
| *Babesia duncani* Infection | 41 | 0 | 0 | |
| Human monocytic ehrlichiosis | 5 | 0 | 0 | |
| Total False (+) | 0 | **3** | **3** | **5** |
| Total True (-) | 212 | 209 | 209 | 207 |
| **Specificity** | | **98.6%** | **98.6%** | **97.6%** |

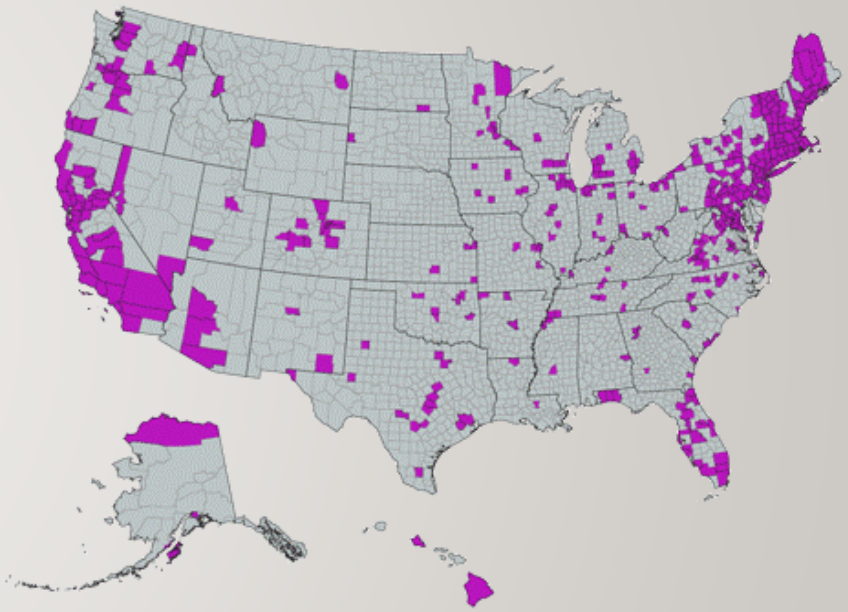
# BORRELIA TESTING RECOMMENDATIONS

- Must use tests that can detect the broadest range of species
  - Lyme - Include testing for all Bb sl
  - TBRF - Multiple species are being seen and all must be included
- RECOMMENDATION: test by combining multiple methods
  - ImmunoBlots for both Lyme and TBRF, + Culture (cePCR)
  - Add the IGXSpot T-cell response assay if a B-cell functional deficit is suspected or known to be present
  - Biopsies with PCR testing when appropriate - synovia, placenta, skin
  - Option to add urine antigen testing

# BARTONELLA - DOCUMENTED IN AT LEAST 49 STATES

Extremely common in Lyme/TBD patients

- Over 45 species known to exist!!
  - Therefore multispecies testing is critical
- Major biofilm builder
- 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 - CLINICAL PICTURE

- CNS - irritates and stimulates the CNS
  - Anxiety, insomnia, tremors, ataxia, seizures, panic attacks, rage attacks, antisocial behavior, depression, hallucinations, schizophrenia, dementia
- Eyes - uveitis, retinitis, retinal artery and vein thromboses
- Regional lymphadenopathy
- Connective tissues: tender nodules (sub-Q, along fascia), sore soles, tendonitis, bone pain, painful joints without synovial swelling
- Peculiar skin manifestations
  - "Bartonella tracks" (like atypical stretch marks)
  - "Bacilliary angiomatosis" (red bumps that may scab)
- GI involvement
  - Gastritis (mimics H. pylori), mesenteric lymphadenitis, peliosis hepatis

# BARTONELLA TESTS – PART 1

- INDIRECT TESTS
- IFA - old technology; designed to detect one species (henselae or quintana). Many false negatives and some false positives
- ImmunoBlot (IGeneX): More sensitive and designed to detect multiple species
  - All culture-positive samples were IB + (100%)
  - Specificity study with 34 unknowns from TBD patients, specificity was 100%
- T-cell stimulation assay (IGXSpot - IGeneX)- genus-level detection of T-cell reactivity, indicating prior exposure

# BARTONELLA TESTS – PART 2

- DIRECT TESTS
- FISH (Fluorescent in-situ hybridization) - Direct visualization via fluorescent RNA probe; is genus-level thus offers extended species coverage. *Also can detect Bartonella hidden in biofilms*
  - Inclusivity study - able to detect all tested Bartonella species (6, plus an atypical)
  - Specificity study - No cross reactivity with any other common TBD pathogen, nor with Plasmodia or Trypanosomes
- Culture (cePCR - IGeneX) - increases sensitivity and overcomes many of the technical limitations of standard PCRs; genus-level detection allows for broad coverage

# BARTONELLA TESTING - RECOMMENDATIONS

Notoriously difficult to detect!

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

RECOMMENDATION: Test by combining multiple methods

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

# BABESIOSIS

Malaria-like intra-erythrocytic parasite

- Is the most common co-infection in Lyme patients
- Look for: fever, sweats, headache, air hunger, cough, profound fatigue, balance issues, and cognitive dysfunction
- Many other symptoms that overlap with Lyme and TBRF
- Low-grade hemolysis can lead to iron-deficiency
- Transfusion transmission and maternal-fetal transmission
- The two dominant species in the USA are B. microti and B. duncani
- B. MO-1, B. divergens, B. odocoilei, and $\geq$3 others are also occasionally seen
- Rarely, atypical Apicomplexa can be found in humans

# BABESIA ODOCOILEI

B. odocoilei - controversial!

- Found in many ticks all across North America
- Published case reports - cases found in USA and Canadian patients, confirmed with 18s sequencing
- Multiple IFA -stained patient samples said to indicate odocoilei
- But a series of 460 Babesia-positive patient samples had DNA sequencing- did not find ANY B. odocoilei
- Confusion may relate to which primer sets are being used for PCR and sequencing, and/or nonspecificity of the IFA stain
- Immunoblot data shows a significant percentage of Babesia species in human patients are not microti or duncani. Could these be divergens and/or odocoilei?

# BABESIA TESTING

- Stained blood smear **-** Done in hospitals - only useful within first week of infection. Limit of detection 0.5% of RBCs infected
- FISH - Blood slides target specific rRNA sequences using fluorescent probes
  - Far more sensitive than standard smear; L.O.D. 0.001%
  - Can detect organisms in biofilms; genus-level test so has broad coverage
- Immunoblot - Far more sensitive than IFA and offers broad species coverage; Validation studies: 100% specificity
- T-cell response assay (IGXSpot - IGeneX) - Genus-level so offers multispecies coverage
- Culture (cePCR) - is a genus-level test so it can detect at least microti and duncani - (and others have been detected too)

# BABESIA TESTING - RECOMMENDATIONS

Notoriously difficult to detect!

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

Testing by combining multiple methods is recommended

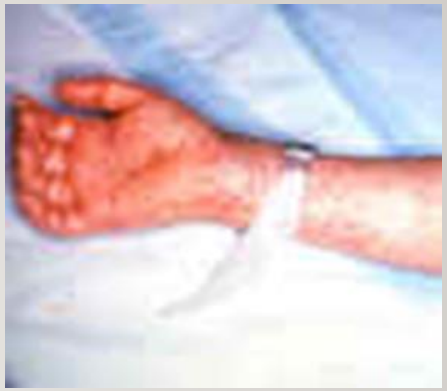
- ImmunoBlot + FISH + Culture (cePCR)
- If there is a known B-cell functional defect, add a T-cell response assay

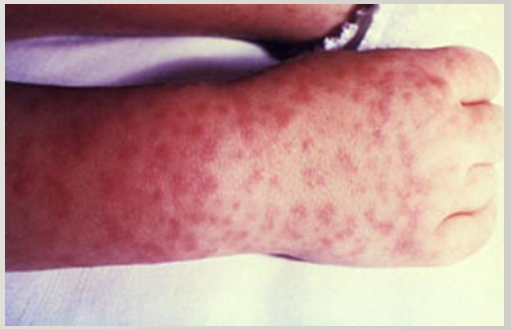
# RICKETTSIA FAMILY

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

Anaplasma, Ehrlichia, and Rocky Mountain Spotted Fever

- CAN BE FATAL!!
- Acute fever, headache, myalgias, malaise
- 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%)





# 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

# CLINICAL GUIDE

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

# TESTING GUIDE

| TEST | METHOD | FEATURES | WHEN TO USE | ACCURACY |
|---|---|---|---|---|
| **IFA, ELISA, WB** | Serology | Single species | Not recommended | False negatives<br>False positives |
| **ImmunoBlot** | Serology | Recombinant Ag's<br>Multiple species | All stages | Maximal |
| **T-cell response assay** | Mitogen stimulation assay | Limited time window | Early and<br>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 and CSF | 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 |

# CHALLENGES IN THE MANAGEMENT OF THE MAJOR TBDS

- Must correct the “terrain” or treatment will be less effective and more difficult to tolerate
- Antibiotic resistant persister bacteria (Borrelia, Bartonella) have been described, leading to treatment failures and to complex and difficult multi-drug regimens
- Treatment-resistant Babesiosis is increasingly being noted
- Labs are seeing higher numbers of Rickettsia-Ehrlichia-Anaplasma infections and treatment options are limited
- Opportunistic infections are common - Mycoplasma, Chlamydia, viruses, yeasts, others

# TERRAIN: NEED TO RESUSCITATE THE PATIENT BEFORE BEGINNING ANTIMICROBIALS

- Chronic inflammatory diseases negatively impact metabolism, detoxification, hormone response and immunity
- Dysbiosis, mucosal inflammation, leaky gut, thick gut biofilms with entrapped viruses all must be addressed
- Multi-faceted approach:
  - Nutritional support, detoxification, immune support, manage inflammation, target infections

# BOTANICALS AS FOODS

- High in balanced vitamins, minerals, amino acids
- Antioxidant content / nutritional content
- Antimicrobial, antifungal, antiviral, antibacterial, vermifuge, purgative – all corrective properties
- A singular herb has multi-faceted applications
- Synergistic ability when used in a combination / formula
- Accepted by cells as fuel because botanicals / herbs are food
- Supports organ function
- Limits need for large protocols

# BOTANICAL MANAGEMENT

- Use of “umbrella-like”, synergistic herbal formulas aimed to support:
  - Balancing of microbial overgrowths
  - Detoxification
  - Organ function
  - Immune function
  - Reduction of inflammation
  - The assimilation and absorption of nutrients
  - The body by offering healing properties delivered via botanical remedies
  - The body in the delivery of plant enzymes

# SYMPTOMS = OVERFLOWING

- Patient symptoms are analogous to an overflowing sink, tub, or toilet
- Toxicity must be reduced (detoxification and drainage support) before attempting to work with the existing microbial burden
- Toxicity may include mycotoxins, heavy metals, pesticides, chemicals, and more
- Approaches include slowing down the faucet (reducing antimicrobial dosing) and/or opening the drains (detoxification and drainage support)
- Base of any chronic illness protocol should always include detoxification and drainage support

# DETOXIFICATION AND DRAINAGE SUPPORT

- Every chronic illness protocol should be built on the foundation of detoxification support
- Both binders (detoxification) and drainage are used to optimize outcomes
- As a starting point for supporting detoxification and drainage, practitioners may use one of the following combinations:



# INFLAMMATION AND IMMUNE MODULATION

- Supporting the reduction of systemic and GI inflammation is often key to improving tolerance of protocols
- May be done with CYFLACALM II™ for neuroinflammation or GI inflammation support; or with MAST-EASE® if the inflammation is driven by MCAS / histamine issues
- Supporting the modulation of a hypervigilant immune system or autoimmune response with IMN-CALM® may also help with improving protocol tolerance and reducing inflammatory burden

# VIRAL SUPPORT FORMULAS

- Many chronic viruses may contribute to chronic illnesses including HSV, HHV, EBV, CMV, VZV, Coxsackie, and others
- Many of the symptoms of chronic illness may be the result of underlying viral activation
- Beyond Balance® has created several formulas (IMN-V®, IMN-V-II™, IMN-V-III™, IMN-V-IV™, and others) to support those dealing with chronic viral activity
- Each formula has a specific purpose in terms of the types of viral support provided; though the formulas are also broad in the support conveyed
- In some cases, more than one viral support formula may be used at a time

# GI SUPPORT FORMULAS

- Some may need to address GI dysbiosis and GI inflammation early on in a protocol with tools such as IMN-GI™, IMN-B™, IMN-B-II™, and CYFLACALM II™
- Chronic GI dysbiosis, SIBO, SIFO, and related conditions are common factors in those with complex, chronic illnesses
- In some, the GI dysbiosis may be parasitic (SIPO) in nature and may consist of protozoal or other parastic overgrowths
- Beyond Balance® offers several tools to support those dealing with protozoan or parasitic activity such as MC-PZ®, PRONAN™, PARAZOMIN™, and PARALLEVIARE®


# BACTERIAL PERSISTERS - BORRELIA AND BARTONELLA

- After exposure to antibiotics, not all bacteria die even in the presence of antibiotics that should work
- Is a programmed shift to an altered metabolic state- non-dividing, hibernating organisms ("stationary phase")
- The microbes are still antigenic, still secrete multiple bioproducts, and still will activate the immune cascade resulting in ongoing symptoms
- Once antibiotics are removed, persisters may revert to active growth
- Antibiotics traditionally kill only growing organisms and rarely kill stationary ones

HINT: if the patient is seronegative but culture or PCR positive, then persisters are more likely (Embers primate study)

# APPROACH TO TREATING SUSPECTED STATIONARY PHASE PERSISTERS

Option #1

- Pharmaceutical regimens that target stationary phase and biofilm persisters all include complicated regimens utilizing multiple antibiotics, many of which can be toxic and need monitoring

Option #2

- Botanicals have been demonstrated to target stationary phase and biofilm persisters and if applied properly, these regimens may replace toxic pharmaceuticals

Option #3

- Use both!

# BORRELIA AND BARTONELLA SUPPORT FORMULAS

- Due to the complex plant constituents found in herbs, herbal formulas are often an ideal tool for mitigating the various morphological forms of an organism
- MC-BB-1® may be supportive for those dealing with Lyme Borrelia; MC-BB-2™ may be supportive for those dealing with TBRF Borrelia
- MC-BAR-1®, MC-BAR-2™, and MC-BAR-3™ were created to support those dealing with symptoms associated with Bartonella
- Bartonella is often one of the more challenging organisms to address; thus, strong detoxification and drainage support are strongly recommended before starting to use these formulas


# BABESIOSIS - USING BOTANICALS

- Babesia - resistance to pharmaceuticals is becoming more widespread
- Recent published studies have demonstrated excellent results in Babesia culture systems of several botanicals
- When carefully applied, botanicals may be better tolerated than most anti-Babesia prescription meds
- Adding botanicals to pharmaceuticals may increase their efficacy and/or allow for regimens that are easier on the patient

# BABESIA SUPPORT FORMULAS

- Babesia is a common co-infection in those dealing with Lyme disease
- It is a protozoan organism that impacts red blood cells
- Beyond Balance® has formulated three products to support those dealing with Babesia; MC-BAB-1®, MC-BAB-2®, and MC-BAB-3™
- Each of the Babesia formulas is intended to support specific types of Babesia
- Over the course of treatment, some practitioners may use more than one of these formulas in a given patient

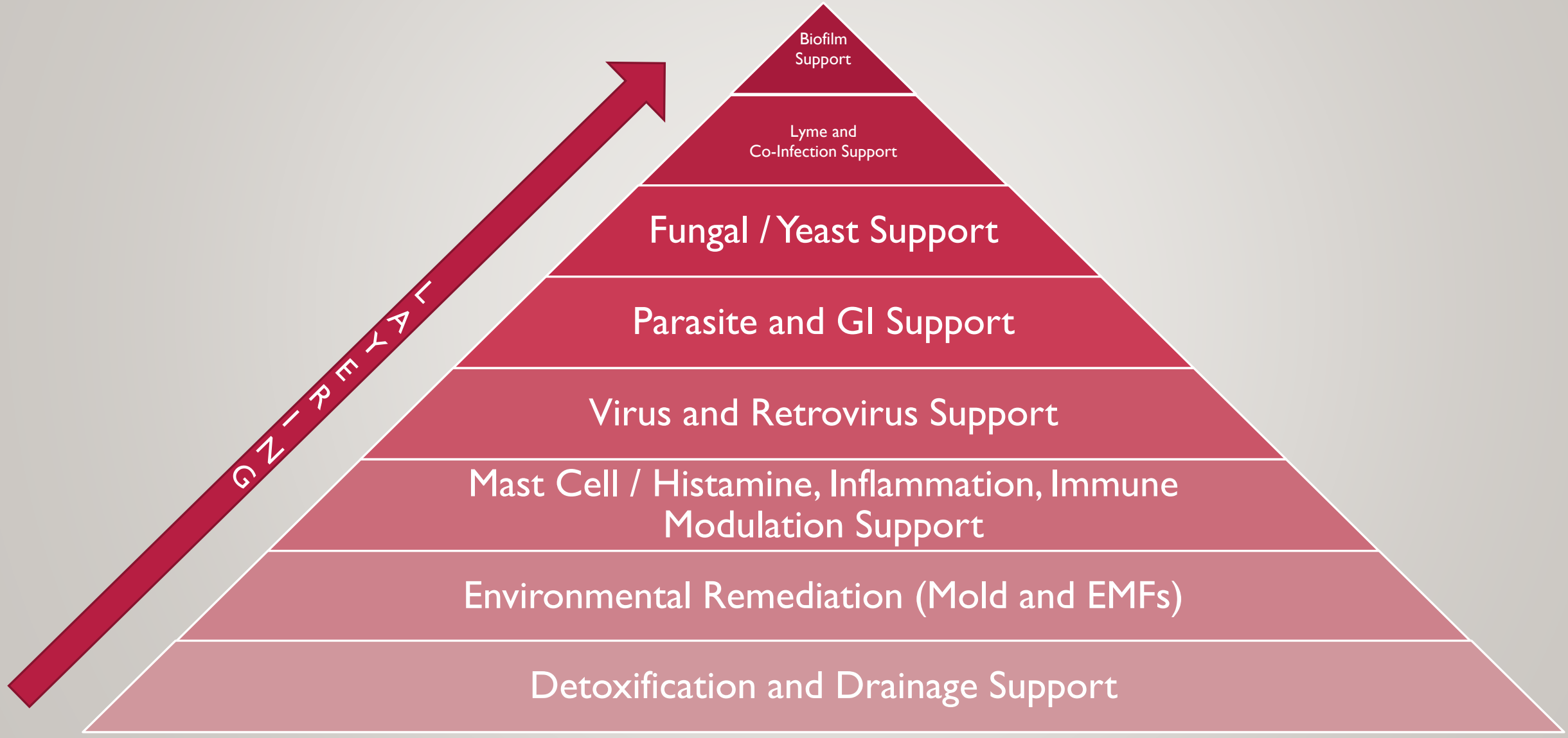
# ADDITIONAL SUPPORT FORMULAS

- ENL-MC® was formulated to support the body's natural defenses against Mycoplasma-like organisms
- MC-CH™ has been formulated to offer support to the immune system's natural ability to guard against microorganisms in the Chlamydia family
- MC-REA® is an immunosupportive formula that may be helpful for those coping with the challenges of Rickettsia, Ehrlichia, and Anaplasma
- These formulas are more targeted formulas often used later in a protocol

# BIOFILM SUPPORT FORMULAS

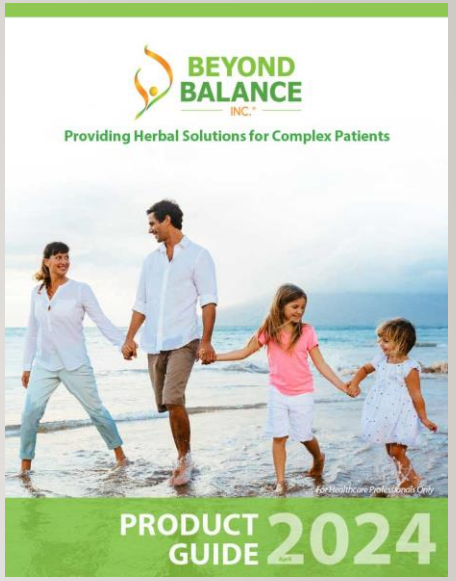
- MC-BFM-P™ and MC-BFM-1® formulas may affect the breakdown and prevention of biofilm activity in the body
- Incorporates guggul to support the emulsification of the fatty component of biofilms
- MC-BFM-P™ is intended for use in the pediatric population
- MC-BFM-1® is a stronger version of MC-BFM-P™ and intended for use in adults; though many adults also start with MC-BFM-P™
- Biofilm formulas are intended to be used late in a protocol and for a short duration (6-12 weeks)
- Continued support for detoxification and drainage as well as any anticipated remaining microbial burden is essential when using these formulas

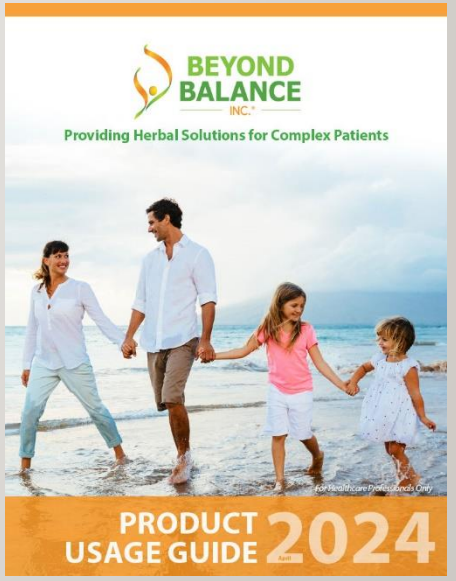
# LAYERING / TREATMENT ORDER



# ADDITIONAL INFORMATION

- Beyond Balance® products are available through licensed and certified healthcare practitioners only
- Dosing guidelines are provided to practitioners through our product guides
- Product training, support, and educational webinars are available to all Beyond Balance® practitioners
- For patients looking for a practitioner who uses the Beyond Balance® formulas, visit our website and select Contact -> Find a Practitioner
- For those looking to open a practitioner account, visit our website and select Register -> Professional
- For additional information, visit BeyondBalanceInc.com



# QUESTIONS?