ILADS

LYME DISEASE AND OTHER TBD'S

Designing Individualized Treatment Regimens Based On Symptomatology and Testing

Richard I. Horowitz, MD

Hudson Valley Healing Arts Center

Hyde Park, NY

845-229-8977

LD & Co-Infections:

Designing Individualized Treatment Regimens

- Chronic Lyme Disease must be seen in the light of multiple tick borne diseases, including HME, HGE, Babesia, Bartonella, Mycoplasma, Chlamydia, RMSF, Q-Fever, Tularemia, and Viral infections (HHV6, HHV8, ? West Nile).
- Symptoms of these diseases overlap and many patients who have chronic ongoing symptomatology who have failed classical therapies for Lyme Disease may improve once all co-infections are diagnosed and adequately treated.

Investigative Treatment Protocols for Lyme Disease and Multiple Co-infections

Immune dysregulation:
ANA+, HLA DR4 +
Plaquenil
?Herbs / CAM tx

Tetracyclines

Cleocin & Quinine
Mepron&Zithromax
Lariam
Artemesia
Malarone

Candida: Nystatin, Diflucan, Acidophilus
?Leaky Gut
?Food Allergies
?El syndrome,
Heavy metal toxicities
?Multiple chemical sensitivities
Hormonal d/f

Borrelia burgdorferi

Ehrlichia/Anapl.

Babesia

Bartonella

Viruses

? Mycoplasma
? Chlamydia

Cell Wall:
Penicillin /
Cephalosporins

Cyst: Flagyl/Plaquenil

Macrolides / Ketolides

Rifampin

Septra/Bactrim

Quinolones

?Neurotoxins
?HBOT
?Heat Therapy
?IV Glutathione

Anti-Virals

Therefore, drug regimens which are effective against multiple organisms simultaneously and penetrate intracellularly and into the CNS may be necessary to achieve significant clinical improvement.

Chronic Lyme Borreliosis Syndrome

- Bb can persist in the body despite extensive courses of antibiotics
- A single tick bite can transmit multiple co-infections (bartonella, babesia, ehrlichia, mycoplasma), which may not be found on standard IFA testing.
- Many of the co-infections are intracellular, protecting them from short courses of antibiotics, making them difficult to eradicate
- Immune dysfunction / autoimmune overlap may be common secondary to molecular mimicry, BLPs, Blebs, HLA status
- Neurotoxins (QUIN) / Bacterial toxins (Bb Tox1) may be responsible for ongoing symptoms.

Chronic LB Syndrome: Problems with Testing and Treatment

1)Intra and Interlaboratory Variation in LD testing

-Bakken et al. JAMA 1992;268:891-895

-Magnarelli, LA. Laboratory diagnosis of Lyme Disease. Rheum.Dis.Clin. North America 1989; 156;735-745

-There are similar limitations to serological testing for Bartonella, w/ false neg IFA's

-Bergmans et al. J Clin Microbiol 1997

-LaScala et al. J Clin Microbiol 1999

-Similarly, Babesia testing often reveals neg IFA's with positive FISH and or PCR results

Chronic LB Syndrome: Problems with Testing and Treatment

2)Timing of Antibody Synthesis

IGM Ab synthesis is usually not detectable for 2-5 wks and disappears after 2-3 mo, occasionally reappearing later in the disease

False neg tests occur if tested too soon after the initial infection

(Craft JE, et al. Journal of Clin Investigation 1986; 78:934-939)

(Grodzuk, RI, Steere, AC. Comparison of immunoblotting and indirect ELISA using different antigen preparations for diagnosing early Lyme disease. Journal of Inf Disease 1988;157;796-797

Chronic LB Syndrome: Problems with Testing and Treatment

3) False Negatives:

-Antibiotic treatment early in the disease prevents a humoral immune response

(Shrestha, M. Grodzuk, RI, Steere, AC: Diagnosing Early Lyme disease. Amer JNL of Medicine, 1985; 78:235-240)

-The same problem may exist for co-inf's explaining the rate of low positive IFA's

-Some co-infections, ie M. fermentans can only be found on PCR, and may require multiple sets before obtaining a positive result

Chronic LB Syndrome: Problems with Testing and Treatment

4)Failure to detect Antibodies

Bb antibodies can be bound in circulating immune complexes, explaining the high false negative rate of antibody testing in the spinal fluid of Lyme pts w/ signif CNS dx.

The immune complex dissociation assay may reveal Bb specific Ab in pts w/ enceph whose CSF otherwise tests normal. Routine use of this assay is not being performed.

(Coyle, et al. Detection of Bb antigens in CSF. Neurology 1993;43:1093-1097)

Chronic LB Syndrome: Problems with Testing and Treatment

5) Biology of the Organism

A)Long replication time

B)Plasmids

C)Blebs → bind free circul Bb Ab, have potent mitogenic activity that ↑ immune activation

D)Cloaking → Bb also surrounds itself w/ the body's lymphocytic proteins, ↓ immune recognition

(Coyle, PK et al. Detection of Bb antigens in CSF. Neurology 1993;43:1093-1097

Dorward, et al. Jounal of Clin Microbiol 1991;29:1162-1170

Barbour, A. Univ of Texas Health Sciences Center, San Antonio, Texas. Borrelia's strategies for survival: Implications for Chronic Disease.)

Chronic LB Syndrome: Problems with Testing and Treatment

6) Suppressed Immune Response

A) In vitro proliferative responses of lymph's to mitogens and antigens were suppressed in the presence of Bb Ag preparations, and IL-2 prod. was inhibited by spirochetes

(Dr J.W. Chiao, Prof of Medicine and Immunol at NY Med Coll. Abstract, 7th Intl Conf on Lyme Borreliosis, 1994)

B) B and T cell Destruction: David Dorward, PhD, Rocky Mtn Labs. 9th Intl. Conf on Lyme Borreliosis.

-lack of lysosomal fusion, destruction of lymph's within 1-3 hrs after incubation

C) Concurrent co-inf's may also suppress immune (f)

-Krause, PJ. Et al. Concurent Lyme Disease and Babesiosis. Evidence for Increased Severity and Duration of Illness

JAMA, June 5,1996; Vol 275, No 21, 1657-1660

Chronic LB Syndrome: Problems with Testing and Treatment

Sequestration in Antibiotic and Immunologically Priviledged Sites

- Skin/ fibroblasts (Klempner)
- Eye (Preac-Mursic, Meier)
- Ligamentous tissue (Haupl)
- Joints (Priem, Bradley, Fitzpatrick)
- CNS (Coyle, Leigner)
- Endothelial cells and macrophages (Ma et al, Infect Immun 1991 Feb;59(2):671-8; Malawista SE et al, J Immunol 1993 Feb 1;150(3):909-15)

Chronic Persistent Infection with Bb Despite Intensive AB's

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Persistence of Lyme Borreliosis

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Chronic Persistent Infection with Bb Despite Intensive AB's

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- Fraser DD, et al. Molecular detection of persistent Borrelia burgdorferi in a man with dermatomyositis. Clinical and Exper Rheum. 1992;10:387-390
- Fried MD et al, Borrelia burdorferi persists in the gastrointestinal tract of children and adolescents with Lyme Disease, JNL of Spirochetal and Tick-borne Diseases, Spring/Summer 2002; 9:11-15
- Fitzpatrick JE, et al. Chronic septic arthrits caused by Borrelia burgdorferi. Clin Ortho 1993 Dec;(297):238-41

Chronic Persistent Infection with Bb Despite Intensive AB's

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- Hassler D, et al. Pulsed high-dose cefotaxime therapy in refractory Lyme Borreliosis (letter). Lancet 1991;338:193

Chronic Persistent Infection with Bb Despite Intensive AB's

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Persistence of Lyme Borreliosis

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Persistence of Lyme Borreliosis

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Persistence of Lyme Borreliosis

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Persistence of Lyme Borreliosis

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Persistence of Lyme Borreliosis

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Persistence of Lyme Borreliosis:Atypical Forms/Cystic Forms

- Preac-Mursic, V et al, Formation and Cultivation of Borrelia burgdorferi Spheroplast-L-form Variants, Infection 24 (1996);No 3:218-26
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Persistence of Lyme Borreliosis:Atypical Forms/Cystic Forms

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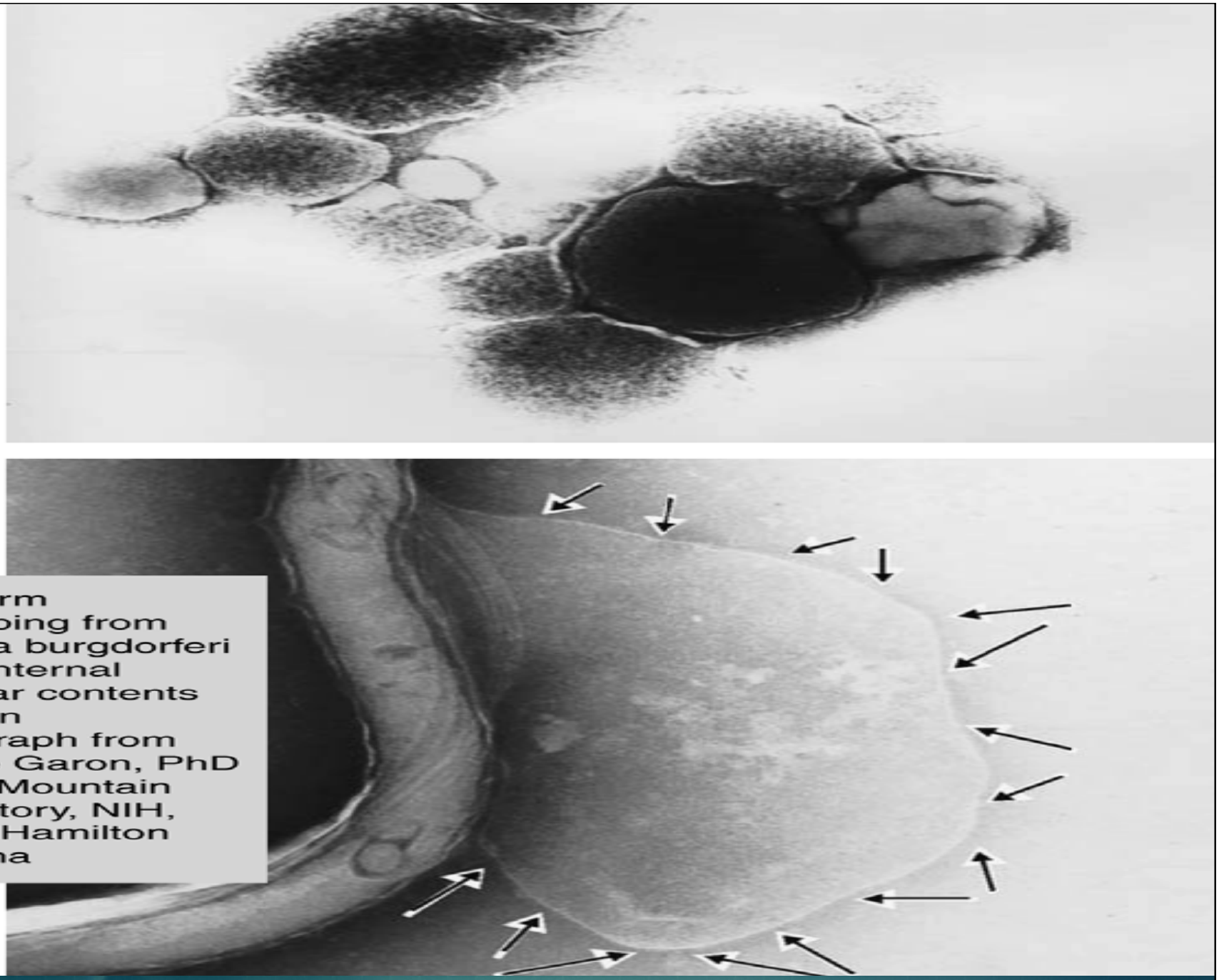
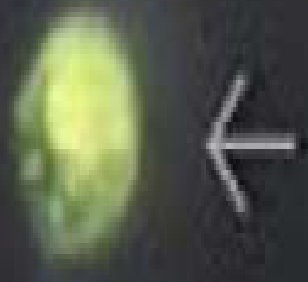
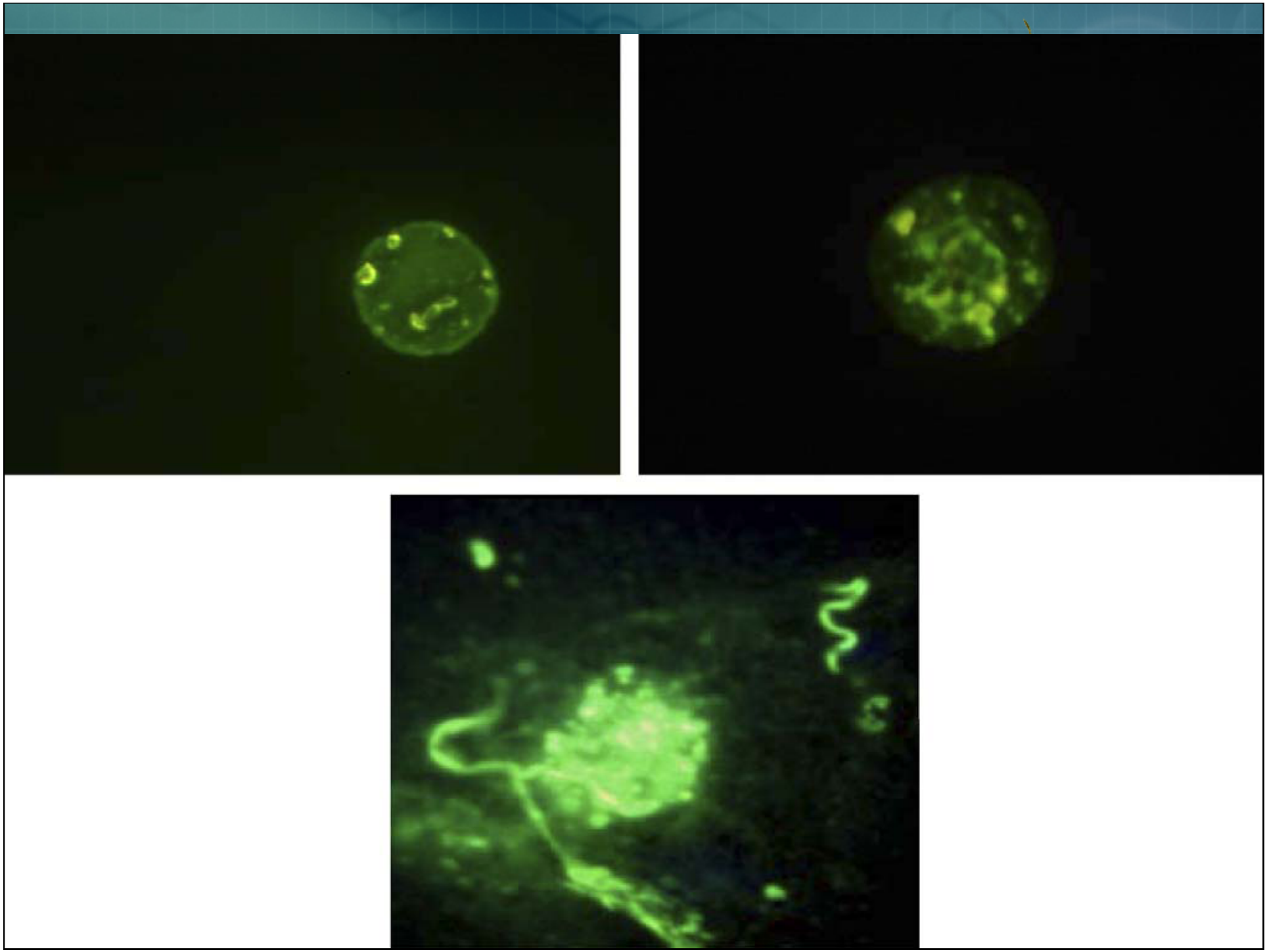


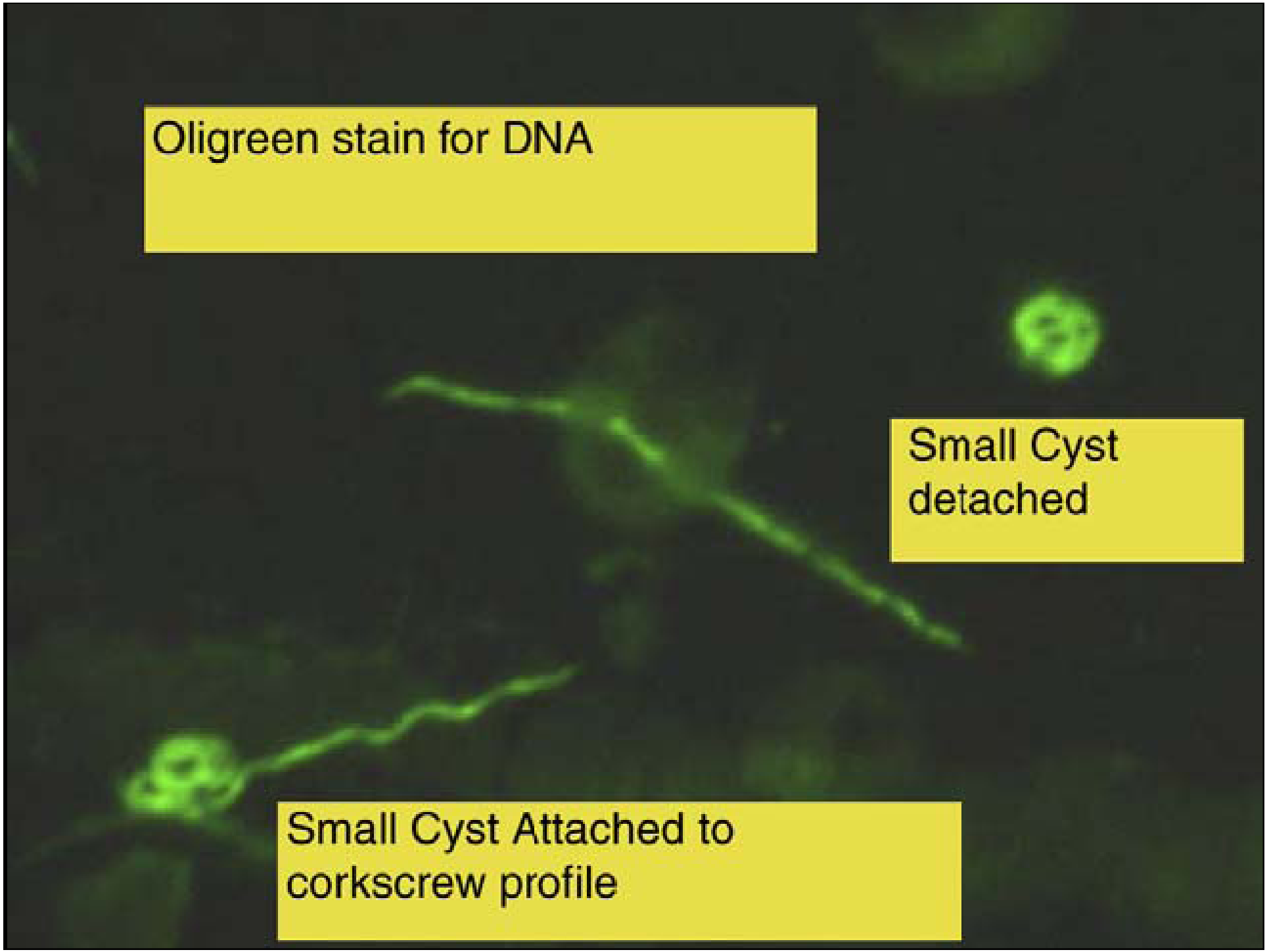
Cyst form developing from Borrelia burgdorferi
Note: Internal floccular contents
Electron micrograph from Claude Garon, PhD
Rocky Mountain Laboratory, NIH, NIAID, Hamilton Montana

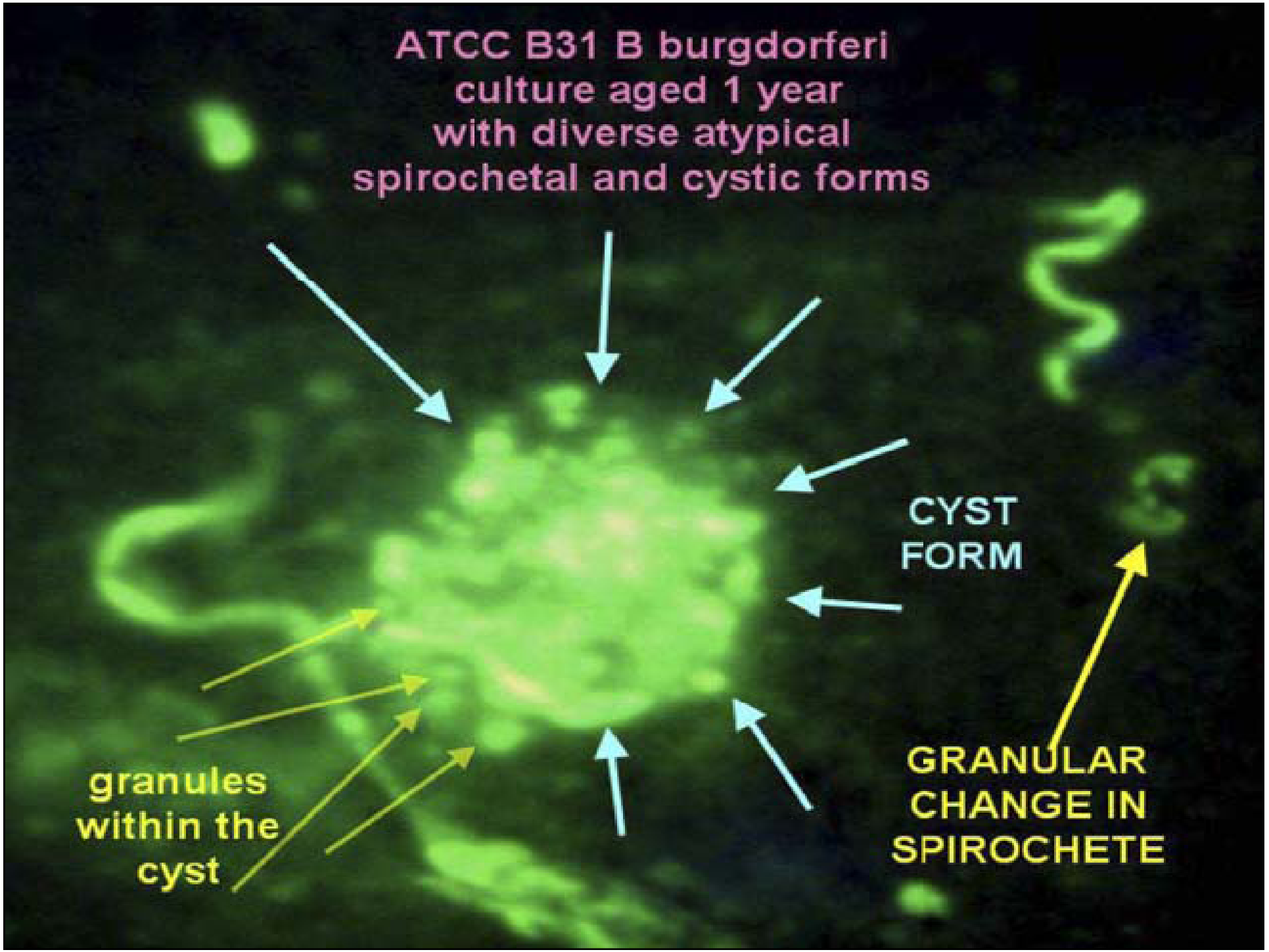
Borrelia cyst form
Note the internal granular elements



Borrelia cyst form




Oligreen stain for DNA
Small Cyst detached
Small Cyst Attached to corkscrew profile


ATCC B31 B burgdorferi
culture aged 1 year
with diverse atypical
spirochetal and cystic forms
CYST
FORM
granules
within the
cyst
GRANULAR
CHANGE IN
SPIROCHETE

Treatment Relapses and Failures with Short-term Therapy

- Logigian (1990) : After 6 mo's of therapy, 10/27 patients treated with IV AB's relapsed or had treatment failure.
- Pfister (1991) : 33 patients with neuroborreliosis were treated with IV AB's. After a mean of 8.1 months 10/27 were symptomatic and borrelia persisted in the CSF in 1 pt
- Shadick (1994) : 10/38 pts relapsed (5 with IV) within 1 year of treatment, and had repeated AB treatment
- Asch (1994) : 28% relapsed w/ major organ involvement 3.2 years after initial treatment
- Valesova (1996) :10/26 relapsed or progressed at 36 mo
- Trieb (1998) : >50% pts symptomatic after 4.2/+/- 1.2 yrs
- Shadick (1999) : 69/184 (37%) report a previous relapse

Benefit of Longer treatment Regimes for Disseminated Lyme Disease

1. Wahlberg,P. et al, Treatment of late Lyme borreliosis. J Infect, 1994. 29(3): p255-61 → 31% improved w/ 14 d Rocephin, 89% improved w/ Rocephin + 100d of Amox and Probenecid, 83% improved w/ Rocephin, then 100 days of cephadroxil
2. Donta, ST., Tetracycline therapy for chronic Lyme disease. Clin Infect Dis, 1997. 25 Suppl 1: p.S52-6.

   → 277 pts with chr LD treated between 1-11 mo: 20% cured, 70% improved, 10% treatment failure

Benefit of Longer treatment Regimes for Disseminated Lyme Disease

3. Oksi, J et al., Comparison of oral cefixime and intravenous ceftriaxone followed by oral amoxicillin in disseminated Lyme borreliosis. Eur J Clin Microbiol Infect Dis, 1998. 17(10) :p 715-9

→ 30 pts w/ chr Lyme treated for 100 d, 90% w/ good or excellent responses

4. Oksi, J., et al. Borrelia burgdorferi detected by culture and PCR in clinical relapse of disseminated Lyme borreliosis. Ann Med, 1999. 31(3):p.225-32

→ 32/165 pts w/ disseminated Lyme treated for 1 or more months of AB's showed that even > 3 mo of treatment may not eradicate the spirochete, longer term therapy may be necessary

Positive Response on Retreatment for Chronic Lyme Borreliosis

- Fallon, BA., et al, Repeated antibiotic treatment in chronic Lyme disease. J Spirochet Tick Borne Dis, 1999. 6(Fall/Winter):p 94-101

→ 18 pts retreated w/ either IV, IM, or oral AB's scored better on measures of cognition. Those retreated w/ IV had the greatest improvement.

- Donta, ST., Tetracycline therapy for chronic Lyme disease. Clin Infect Dis, 1997

→ 98 pts retreated w/ either tetracycline, hydroxychloroquine and a macrolide, or IV ceftriaxone showed rates of cure or signif improvement of 98%, 74%, or 85% respectively.

Positive Response on Retreatment for Chronic Lyme Borreliosis

- Oksi, J., et al., Borrelia burgdorferi detected by culture and PCR in clinical relapse of dissseminated Lyme borreliosis. Ann Med, 1999. 31(3):p.255-32

→ 13 pts w/ clinical relapse and culture or PCR + were retreated for an additional 4-6 wks w/ IV AB's w/ good response in 69%

- Krupp, L.B., et al., Study and treatment of post Lyme disease (STOP-LD): a randomized double masked clinical trial. Neurology, 2003. 60(12):p1923-30.

→ 55 pts w/ persistent LD treated for an additional 28 d w/ IV ceftriaxone, 64% showed improvement on primary outcome measurement of fatigue

- Cameron, D.J., Lyme Disease Clinical Trial- Effectiveness of Retreatment on Health-Related Quality of Life. Abstract, Lyme & Other TBD's: Emerging Tick Borne Diseases, Fri Oct 28th, 2005, Philadelphia,PA.

Columbia University Study of Chronic Lyme Encephalopathy

- This study of Persistent Lyme Encephalopathy enrolled 37 Lyme patients and 20 age-, sex-, and education matched controls
  - Inclusion Criteria: Age 18-65, CDC+ IgG WB, Prior tx w/ min 3wks IV abx, persistent memory problems
- Each subject had 3 major evaluations at baseline, week 12, and week 24.
  - Self Reported scales of functional status, anxiety, depression, pain, and fatigue
  - Baseline comparisons of MRI and PET measures of Lyme patients to normal controls.
- Study was a 10 week double blind PBO-controlled trial with IV Rocephin followed by 14 weeks on no antibiotics.

Columbia University Study of Chronic Lyme Encephalopathy

- Results:
  - Lyme patients were as sick as pts with CHF
  - Only 1 patient had FMS
  - Minor neurological involvement was common
  - At week 12 (in treatment group):
    - Favored drug regimen vs. PBO
      - Improved fatigue, joint pain, depression, and physical functioning
      - Pet scan showed increased metab. of tx group
      - No sig. effects on MRIs
  - 1st PBO-controlled study showing a significant improvement with long term re-treatment with IV antibiotics (Rocephin).
    - By week 24 there was a loss of gains in cognition and increased fatigue.

★ 60% had +Bartonella IFA and several had +PCR

Ehrlichiosis/Anaplasmosis

Symptoms	Testing	Treatment
• Tick-borne febrile illness, most commonly characterized by acute onset with: -HA -Myalgias -Malaise	-HME & HGE titers and PCRs -Cytopenias – leukopenia, thrombocytopenia - ↑LFT's -Morulae (intracytoplasmic colonies) in WBC, CSF, bone aspirate or biopsy	-Tetracyclines (doxy, etc) -Rifampin

Babesiosis

Symptoms	Testing	Treatment
• ↑↑ severity of sx w/ Lyme Disease -Fevers, chills, flushing, day or night sweats -Fatigue -Joint aches -Paresthesias -Cognitive d/f -HA -↑ Emotional lability	• B. microti -Smear -IFA -PCR (mult. sets) -FISH • WA-1 • ? Other species • Rare: -hemolytic anemia -thrombocytopenia -↑ BUN/Creat • Subclinical presentations more common	-Mepron + Zithro (or other macrolide) -Malarone 100/250 mg 4 qd x 3d then 1 qd thereafter +/- macrolide -Cleocin + Quinine (? ½ dose if full dose not tolerated) -Lariam -Artemesia -Exchange transfusion

Problems with Babesia Testing and Treatment

- The genus Babesia comprises > 100 species of tick-transmitted protozoal pathogens known as piroplasms. Most zoonotic cases are due to B. microti and B. divergens. (B. caballi, B. equi, B. canis, Cytauxzoon felis)
- WA-1 infection is esp. prevalent in Calif. Serologic surveys of N. Calif have shown a high seroprevalence to WA-1 antigens. ? Possibility of transfusion assc Babesia
- WA-1 is more closely related to bovine Theileria parasites than Babesia species
- Theileria parasites are distinguished from Babesia parasites by the presence of an exoerythrocytic schizont stage. They cause lymphoproliferative dx w/ pyrexia, ↑ LN's, panleukopenia and ↓ platelets

Telford,S. et al. Cultivation and Phylogenetic Characterization of a Newly Recognized Human Pathogenic Protozoan. Journal of Inf Dis. 1994;169:1050-6

Problems with Babesia Testing and Treatment

- Patients co-infected w/ Lyme and Babesia show evidence for ↑ severity and duration of illness.

Krause, P.J. JAMA, June 5, 1996; Vol 275, No. 21,

Iacopino V. et al. Life-Threatening babesiosis in a woman from Wisconsin. Arch Int Med. 1990 Jul; 150(7): 1527-8

- Babesia parasites can persist after short term and long term treatment in co-infected LD patients

Krause, P.J. et al. Persistent Parasitemia After Acute Babesiosis. NEJM 1998;339:160-5

Horowitz, RI. Chronic Persistent Babesiosis after Acute Treatment with Cleocin and Quinine, and Atovaquone and Azithromycin. Abstract, 12th Intl Scientific Conference on Lyme Disease and Other Spirochetal & Tick-Borne Disorders. April, 1999. New York City.

Testing For Babesia

Comparison of B. microti FISH and PCR Tests on B. microti IFA Negative Patient's Whole Blood (After Discrepant Analysis)

FISH \ PCR	+	-
+	20	4
-	15	60

N = 99

Sensitivity Rate:

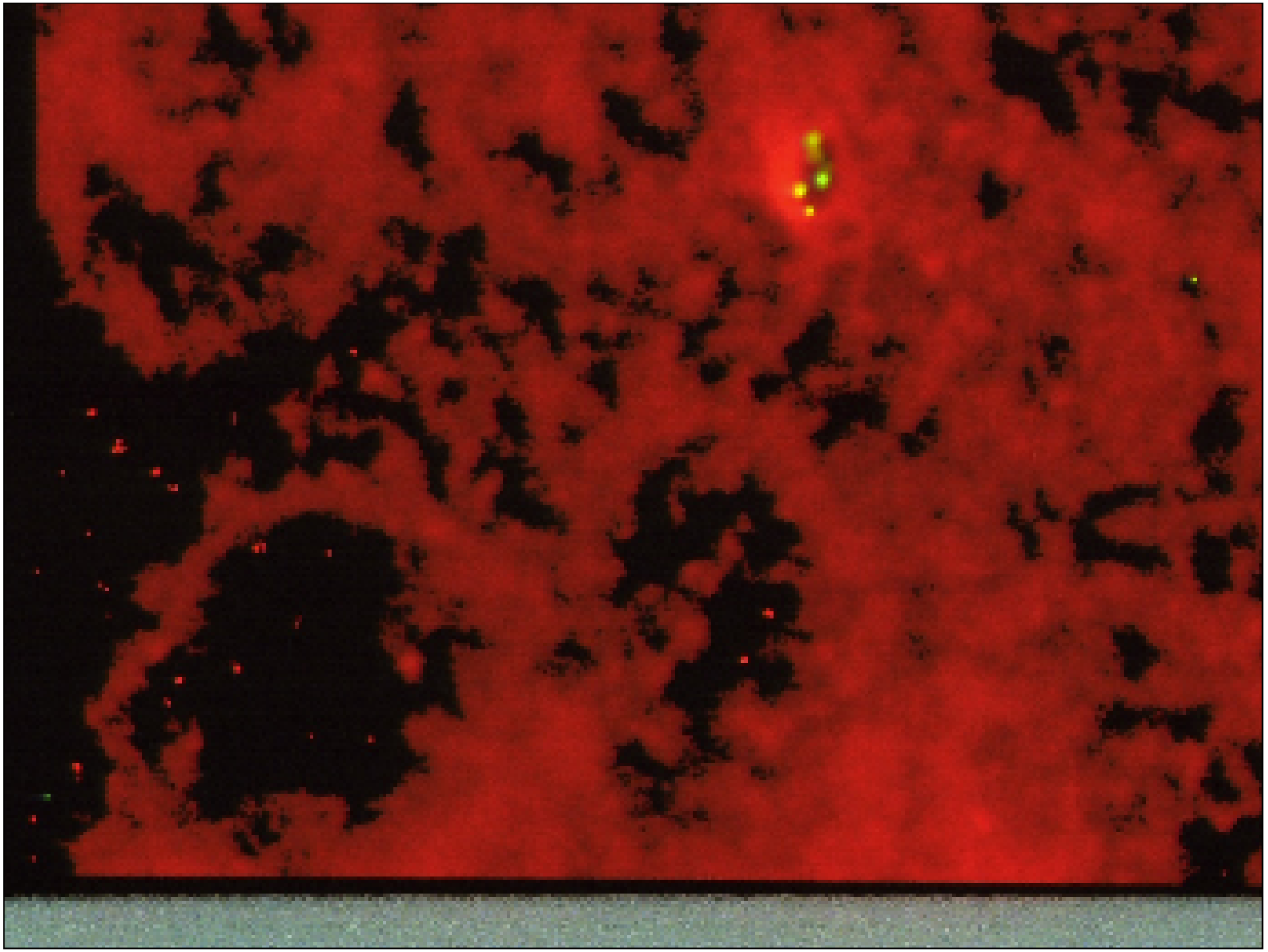
FISH = 29%

pcr = 25%

Total Samples = 210

IFA neg = 99

Sensitivity IFA = 53%



Problems with Babesia Testing and Treatment

- Blood smears and IFA are unreliable in making the diagnosis of Babesiosis. PCR and FISH testing should be used in a panel approach to ↑ sensitivity

Comparison of PCR with Blood Smear and Inoculation of Small Animals for Diagnosis of Babesia microti Parasitemia. Krause, P.J. et al. Journal of Clin Microbiol, Nov 1996, p. 2791-2794

Fluorescent, Ribosomal RNA Probes for Clinical Application: A Research Review. Shah, J. et al. Diagonostics and Clinical Testing, May 1990, Vol 28 p. 41-44

RMSF

Symptoms	Testing	Treatment
• Early clinical pres non-specific • Initial Sx: fever, nausea, vomiting, severe HA, myalgias •Late Sx: rash, abd pain, joint pain, diarrhea •Rash is red spotted petechial rash, > 6th day, only in 35-60%, palms & soles 50-80%	• Thrombocytopenia • Hyponatremia • ↑ LFTs • abnl WBC • IFA for IgM/IgG, IgM ↑ by end of 1st week, IgG ↑ > 1 wk • PCR – most rapid & specific • Immunostaining of skin bx – only 70% sensitivity	• Start immediately based on clinical findings • Doxycycline – continue for at least 3 days until fever subsides, for minimum of days total tx • Alt. tx is Chloramphenicol

Powassan Encephalitis

Symptoms	Testing	Treatment
• Encephalitis: • Can be transmitted in as few as 15 min of tick attachment • Fever, Seizures, focal neuro findings, ↓ consc., hemiplegia, • Sequelae: motor diff, global neuro def, mental status Δ, visual def, hearing impair	• Serum & CSF POW virus-specific IgM, neutralizing ab, ↑ WBC in CSF (1°lymphocytes) • PCR • EEG – diffuse encephalitis • MRI – microvasc ischemia or demyelination	• Supportive • ? HIV meds • Fatality 10-15% • Most infx not result in disease

West Nile Virus

Symptoms	Testing	Treatment
• HA, myalgias, back ache, anorexia, 1 in 5 w/ febrile illness • Roseolar or maculopapular rash on face & trunk in 50% of pts • Gen. Lymphaden. • 1/150 w/ severe CNS involvment: meningoenceph, acute flaccid paralys, movement d/o, ataxia, CN involv, polyradiculopathy	• Mild leukocytosis or leukopenia • Occas hypoNa • CSF: ↑ lymphs mild pleocytosis • Serum or CSF WNV-spec IgM ELISA, PCR • IgG > 7th day • False positive results with Yellow Fever or JE vacc. or had past flavavirus infx (Dengue)	• No established tx • Supportive • ? IV IG • Sequelae: up to 10% mortality if CNS involv., fatigue, chronic HA, memory d/f, diff walking, muscle weakness, depression

Tularemia

Symptoms	Testing	Treatment
• Vary in severity and presentation based on virulence, dose, and site • fever, chills, HA, body aches, coryza, sore throat, pulse-T° disassociation • Respiratory sx (pneumonic), GI (N/V/D), occas sepsis • Oropharyngeal • Ulceroglandular – can be from tick bite • Oculoglandular, etc	• Direct fluorescent antibody • Immunohistochem. stains of secretions, exudates, bx's • Culture • PCR, ELISA, Immunoblotting • Antigen detection assays	• IV/PO Doxy • IV/PO Cipro • IV Streptomycin (DOC) • IV Gentamicin • Chloramphenicol • Treatment failures reported with ß-lactams, & macrolide antibiotics

Q-Fever *(Coxiella burnetii)*

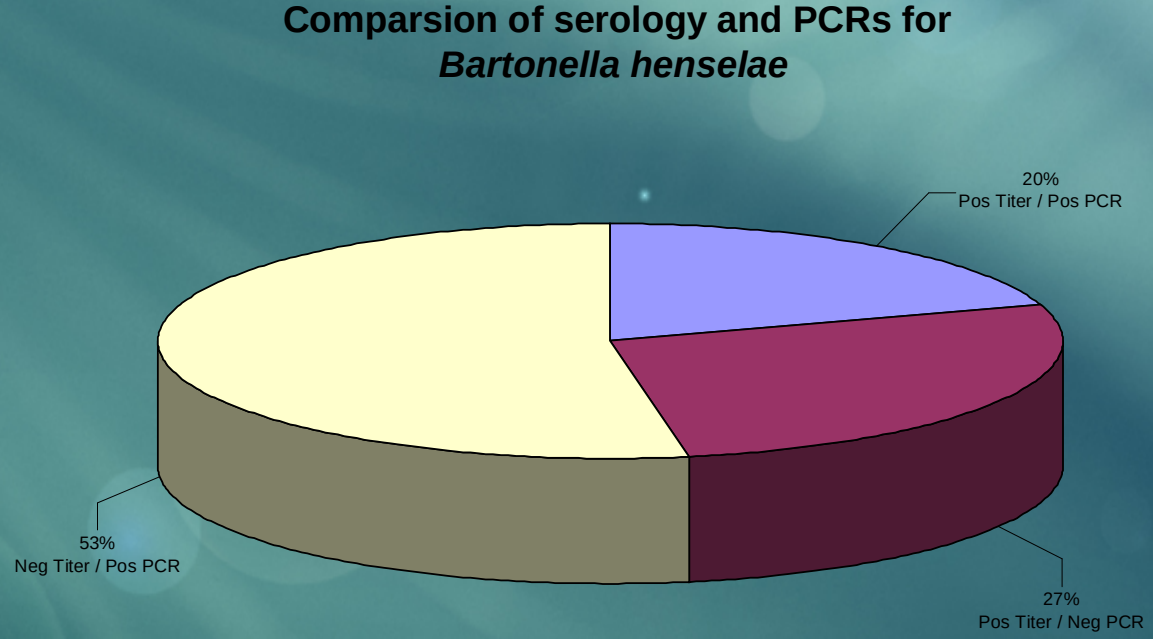
Symptoms	Testing	Treatment
• Only 50% show signs of clinical illness • Acute: high fevers (104-105), chills & sweats, myalgias, severe HA, malaise, abd pains w/ N/V/D, hepatitis, pneumonia, non-productive cough, CP, confusion w/ meningo enceph, PNP, GBS, myelitis, weight loss • Chronic: endocard., can occur 1-20 yrs after infection	• IFA: include IgG/IgA/IgM antibodies • Immunohistochem staining • PCR • Transient decrease in platelets	• Doxycycline (most effective within the 1st 3 days of illness) • Quinolones • For Chronic Q-Fever Endocarditis: Doxy+Quin x 4 yrs or Doxy+Plaq x 1.5-3 yrs.

Bartonella

B. henselae: Cat scratch disease (ticks)
B. quintana: Trench fever (lice)
B. baccilliformis: Carrions disease (sand flies)

Symptoms	Testing	Treatment
<u>Typical manifestations:</u> Papule (rash) / regional lymphadenopathy <u>Atypical manifestations:</u> -Encephalopathy/ chronic demyel. PNP -Radiculitis / Myelitis / Vasculitis -Ophthalmologic manif -Sarcoid like presentations w/ enodosum, arthritis, osteolytic lesions	B. henselae IFA (unreliable) PCR	-Doxy (oral/IV) + Rifampin (+ CQ12) -Quinolones + Tetras or Macrolides -Septra/Bactrim + Macrolides *above regimens generally include Plaquenil 200 mg bid

Comparison of Bh Serology & PCR's



Mycoplasma Fermentans

Symptoms	Testing	Treatment
-? role w/ Lyme & other TBD's -? exacerbating underlying sx -? responsible in part of chronic relapsing sx	-IFA -PCR	-Tetracyclines -Macrolides -Quinolones

Mycoplasma Infections in Chronic Lyme Disease:

A Retrospective Analysis of Co-Infection and Persistence demonstrated by PCR Analysis Despite Long Term Antibiotic Treatment.

16th International Scientific Conference on Lyme Disease

Hartford, CT 2003

Richard I. Horowitz, MD

Dylan J. Rodner, MPAS, RPA-C

Mycoplasma Infections in Chronic Lyme Disease

- **Background:** Patients with chronic Lyme Disease often have multiple co-infections (HME, HGE, Babesia, Bartonella), which may be responsible for persistent ongoing symptoms including fatigue, headache, myalgias, arthralgias, and cognitive difficulties. These symptoms overlap other disease processes such as CFS, FMS, and Gulf War Illness (Nicolson et.al. J. Occup. Environ. Med. 1996;38:14-16) where multiple mycoplasmal infections were implicated to be either causative, co-factors, and/or opportunistic agents in these chronic illnesses (Nicolson et.al. Mycoplasmal Infections in Chronic Illnesses. Medical Sentinel, V4, N5, Sept/Oct 1999, 172-75, 191). Patients with the diagnoses of chronic Lyme Disease and overlapping co-infections with chronic persistent symptoms were therefore screened for the presence and/or persistence of mycoplasmal infections after long term antibiotic therapy.

Mycoplasma Infections in Chronic Lyme Disease

- **Results:** All 27 patients analyzed showed evidence of persistent Mycoplasma fermentans infection by PCR analysis after an average length of antibiotic treatment of 10¾ months. The average patient received 6½ months of macrolide therapy, ¼ month of quinolone therapy, and 4 months of doxycycline therapy. No significant difference was found among the different antibiotic regimens (azithromycin, clarithromycin, dirithromycin, ciprofloxacin, moxafloxacin, and doxycycline). Ongoing symptoms at the end of the study included fatigue (96%), joint pain (93%), cognitive difficulties (78%) and headaches (33%).

Mycoplasma Infections in Chronic Lyme Disease

- **Discussion:** Mycoplasmal infections have been shown to be effective at evading the immune system and synergistic effects with other infectious agents is known to occur (Baseman et.al. Emerg. Infect. Dis. 1997; 3:32-32.). Recommended treatment for mycoplasmal blood infections requires long term antibiotic therapy which usually includes 6 week cycles of doxycycline at 200-300 mg per day (Nicolson et.al. JAMA 1995; 273:618-619.) or ciprofloxacin 1500 mg per day, azithromycin 500 mg per day, or clarithromycin 750-1000 mg per day (Nicolson GL. Intern. J. Med. 1998;1:115-117 and 123-128). Despite recommended treatment regimens however, persistent mycoplasmal infections were demonstrated in this cohort of Chronic Lyme Disease patients. Multiple cycles of antibiotics are required because of their intracellular location, slow growing nature, and inherent insensitivity to most antibiotics (Nicolson 1999).

Mycoplasma Infections in Chronic Lyme Disease

- **<u>Discussion</u>: (**con't) Mycoplasmas have been shown to interact non-specifically with B-lymphocytes resulting in the modulation of immunity promoting autoimmune reactions and rheumatoid diseases (Simecka et.al. Clin. Infect. Dis. 1993;17(Suppl 1):5176-5182). Mycoplasmal infections also increase proinflammatory cytokines including IL-1,2, and 6 (M∫hlradt et.al. Infect. Immunol. 1991;58:1273-1280), and have been found in the joint tissues of patients with rheumatological diseases suggesting their pathogenic involvement (Furr et.al. Ann. Rheumatol. Dis. 1994;53;183-184). Further studies therefore need to be done to elucidate the role of mycoplasmal infections in Lyme Disease patients with chronic persistent symptomatology.

Differential Diagnosis:

When to suspect co-infections with these organisms

A) Lyme Disease: fatigue, headache, arthralgias, cognitive difficulties. Clue - *migratory arthralgias*, symptoms tend to *come and go*, including intermittent paresthesias. Women flare before-during-after menstrual cycle.

B) Babesia: malarial like illness: fever, chills, day sweats, night sweats, persists despite Lyme treatment.

Severity of illness - co-infected patients are the most severely ill.

(JAMA 1996 Krause et.al.: Patients co-infected with Lyme Disease and Babesiosis had evidence for increased severity and duration of illness. Circulatory spirochetal DNA was detected more than 3x as often in co-infected patients as in those with Lyme Disease alone.)

C) Ehrlichia: High fevers, low WBC counts and platelet counts, elevated liver functions.

D) Bartonella: ongoing symptoms despite prior courses of antibiotics (fatigue, headache, resistant arthritis) especially, resistant *encephalopathy* and cognitive difficulties, new onset of a seizure disorder or history of a seizure disorder. *Opthalmological manifestations:* visual loss, neuro retinitis; Significant *lymphadenopathy*. ? GI sx.

E) Mycoplasma / Chlamydia / Viruses: ? Underlying role with resistant sx.

Initial Laboratory Testing & Follow-up

- TBD's: Lyme C6 Elisa, IgM & IgG Western Blot, HME, HGE titers, Babesia IFA, smear, PCR, Fish assay, Bartonella IFA, PCR., Mycoplasma IFA + PCR, Chronic fatigue panel → MDL (Mycoplasma, Chlamydia, HHV-6, HHV-8)
- Routine bloods: CBC, CMP, TFTs + anti-thy ab, B12-folate, Methylmalonic acid-homocysteine levels. If ↑ LFT's → ? Q fever
- Autoimmune Panel: ANA, RF, ESR, C3, C4, CH50, C1Q Immune complexes, HLA DR-2,4
  - (? SS+DS DNA, Sm Ag, Sjogren's SSA, SSB)
- CPK, ACE level, DHEA / Cortisol ratio, Other hormone tests (ie IGF1)
- Immunology Panel: IgA, IgM, IgG & subclasses, Phytohemagluttin studies, Stricker Panel (CD-57 NK Cells)
- Functional Medicine: Heavy Metals → Doctor's Data; 90 Food Allergy Profile, Organix (urine organic acids) → Metametrix; ? 6hr GTT r/o reactive hypoglycemia;
- Difficult diagnostic cases:
  - Serial PCR's for TBD's +/- Mycology Panel → MDL
  - Lyme urine/blood multiplex PCRs, Lyme DOT Blot, RWB → Igenex
  - ? RMSF, Brucella, Q-Fever, Tularemia, WNV

Designing Combination Treatment Therapies

Therapies should be based medical hx, lab testing, TBD's, and underlying symptomatology

- Differential Diagnoses & Treatment:

1. Lyme disease:

-Cell wall drugs: Amoxicillin, Augmentin, Omnicef, Ceftin, Cedax, Suprax, IM Bicillin, IV Rocephin, IV Claforan, IV Vanco, IV Primaxin

-Cystic forms: Flagyl, Tindamax, Plaquenil

-Intracellular forms: Macrolides/Ketolides: Zithromax, Biaxin (XL), Ketek and Doxycyline (Doryx), Minocycline

2. Babesiosis:

-Mepron & Zithro (or other macrolide/ketolide)+/- Septra, Cleocin & Quinine, Malarone, Lariam, Artemesia

Differential Diagnosis & Treatment

3)Ehrlichiosis/ Anaplasmosis :

-Doxycycline, Minocin, Rifampin

4)Bartonellosis:

-Tetra + Quinolone (Levaquin), Tetra + Rifampin, Macrolide + SeptraDS

5) Mycoplasma/Chlamydia: 2 intracellular AB's (tetra + macrolide/or ketolide, tetra +quinolone, tetra + Rifampin...)

6) Other TBD's: RMSF, Q Fever, Tularemia

Differential Diagnosis & Treatment

7) Viruses: EBV, CMV, HIV, W. Nile, HHV6 & HHV8, Hep A,B,C

8) Immune Dysfunction:

-ANA, RF, CCP, ssDNA, dsDNA, SmAg, SSA, SSB, Immunoglob's & subclasses, HLA DR2,4, B27, IL-6, TNF-α, T4/T8, NK57

-Consider immune support (modulator/booster)

9) Systemic Candidiasis/ Leaky Gut/ GI Abn:

-stool for CDSA, yeast, food allergy profiles (IGE and IGG)

-Celiac Dx: TTG, Anti-Gliadin AB, upper endo

-R/O Colitis: GI consult, colonoscopy

Differential Diagnosis & Treatment

10) Multiple Chemical Sensitivity/Mold?
Environmental toxin exposure/ Heavy metal toxicity

-Metametrix:AA/FA profiles, Organix test, lipid peroxide, sulfates, nitrates

-Doctor's Data: 6hr urine DMSA challenge

-Neuroscience Labs

-Mold plates/Stachybotris titers

-Accuchem Laboratory: fat biopsy, blood analysis

Differential Diagnosis & Treatment

11)Food Allergies:

-check local food RAST, Metametrix 90 food allergy profile

12)Parasitic Inf's:

-check stool O+P

13)Neurotoxins/ Brain fog:

-trial IV GSH (oral, nasal, rectal, dermal)

-Questran vs Wellchol & Actos

-Provigil, Namenda, Aricept, PC, PS, Gingko

14)Sleep Disorder w/ Excessive Daytime Somnolence

-Etiology: OSA, Meds, Pain, Nocturia, Depression/Anxiety, RLS → Requip, Gabatril, Trazadone, Lyrica, Xyrem, Remeron, Elavil, Ambien, Roserem, Sonata, Lunesta, L-Theonine, Valerian Root, Herbsom…

Differential Diagnosis & Treatment

15)Reactive Hypoglycemia: 5hr GTT w/ insulin levels

16)Psychiatric Hx/ Hx Drug Use/Addiction

-psych consult: ?hx abuse, somatization d/o

- neuropsych evaluation

-SSRI/Wellbutrin, Cymbalta..

-Meditation, CST, Eidetic therapy, EMDR, NMT, cognitive rehab, Books: The Journey (Brandon Bays)

-Pain management specialist/ detox programs

17)Autonomic Dysfunction: Tilt table test, BP log w/ home BP readings.

-?B blocker, ↑Na diet w/ ↑ fluids, Florinef, Cortef

Differential Diagnosis & Treatment

18)Endocrine & Metabolic Disorders

-check B12, folate, MMA, HC

-Thyroid (f): check T3, T4, T3RU, Free thyroid hormones, TSH, Anti-Thyroglob, Anti-Thyroid peroxidase

-GH: IGF1 levels, L-ARG stimul test

-Testosterone, free test, estradiol, progesterone

-DHEA/Cortisol levels (saliva)

-check neurotransmitter levels

-check intracellular minerals (RBC Mag++)

Differential Diagnosis & Treatment

19) Increased LFT's:

-?AB's, ETOH, Hepatitis, Q-Fever, Hemochromatosis (Fe, TIBC, ferritin)

-Wilsons dx: ceruloplasmin levels

-α1AT deficiency, steatosis, chemical exposure/ pesticide

-Consider use of Silymarin, Hepa#2, NAC, MedCapsDPO

20) General Deconditioning:

-weight training, exercise, PT

Designing Combination Treatment Therapies

- General Antibiotic Guidelines used at the HVHAC:
  1. When first treating a patient with Lyme + other TBD's consider building a regimen around a tetracycline.
  2. If a patient's sx's plateau or worsen, consider changing the regimen or adding a therapy for occult co-infections (ie quinolone, macrolide, rifampin..)
  3. If a tetracycline regimen has not brought adequate clinical improvement consider changing to a regimen including a cell wall drug.
  4. Consider using Plaquenil + Mepron + Macrolide + Septra if concurrent Babesia/Bartonella. Continue w/ Malarone once sweats/chills have significantly ↓
  5. Plaquenil can generally be added to any regimen to help with cystic forms, autoimmune overlap, and raising intracellular pH.
  6. If using multiple antibiotics simultaneously, consider adding nystatin, diflucan, probiotics, and a low CHO/yeast-free diet.

Designing Combination Treatment Therapies

6. If patient experiences significant JH rxns consider an alkaline diet with Lemon-Lime Therapy.
7. Consider IM Bicillin / IV abx when oral abx have failed. Make sure all regimens penetrate into the CNS and intracellular compartments simultaneously.
8. Monitor monthly blood work (CBC, LFTs…)
9. Continue antibiotics until 2 months sx-free to prevent relapses and chronic illness
10. Consider trial off abx and treating for candida / yeast overgrowth after a reasonable course of antibiotics has been tried.
11. Pulsed therapies may be used for antibiotic intolerance, yeast problems, or once significant clinical improvement…

Designing Combination Treatment Therapies: Horowitz Protocol

Evaluate the patient for all TBD's, and rotate the regimens to cover the most common pathogens, ie Lyme, Ehrlichia, Babesia, Bartonella, Mycoplasma

- Use multiple drugs simult. to hit all forms of Borrelia, and address IC infections (gen w/ 2 Intracell AB's)/ CNS
- For the severely ill patient, if multiple IC co-inf's present, consider a cell wall drug (ie Omnicef), w Plaquenil + tetracycline (Minocin, Doryx), + macrolide (Zithromax,) to hit 30S and 50S ribosomal subunits. This regimen will cover cell wall, cystic, and IC forms. After 1-2 months, pulse down the cell wall drug, and add a more potent cystic drug (Tindamax, or Flagyl). Add B6 50mg 3x/day, plus methylcobalamine. Leave the patient on Nystatin, high dose probiotics. For patients with sensitive GI systems, ramp up slowly to GI tolerance. Bicillin can be used or IV Rocephin in the severely ill pt w/ GI intolerance.

Designing Combination Treatment Therapies

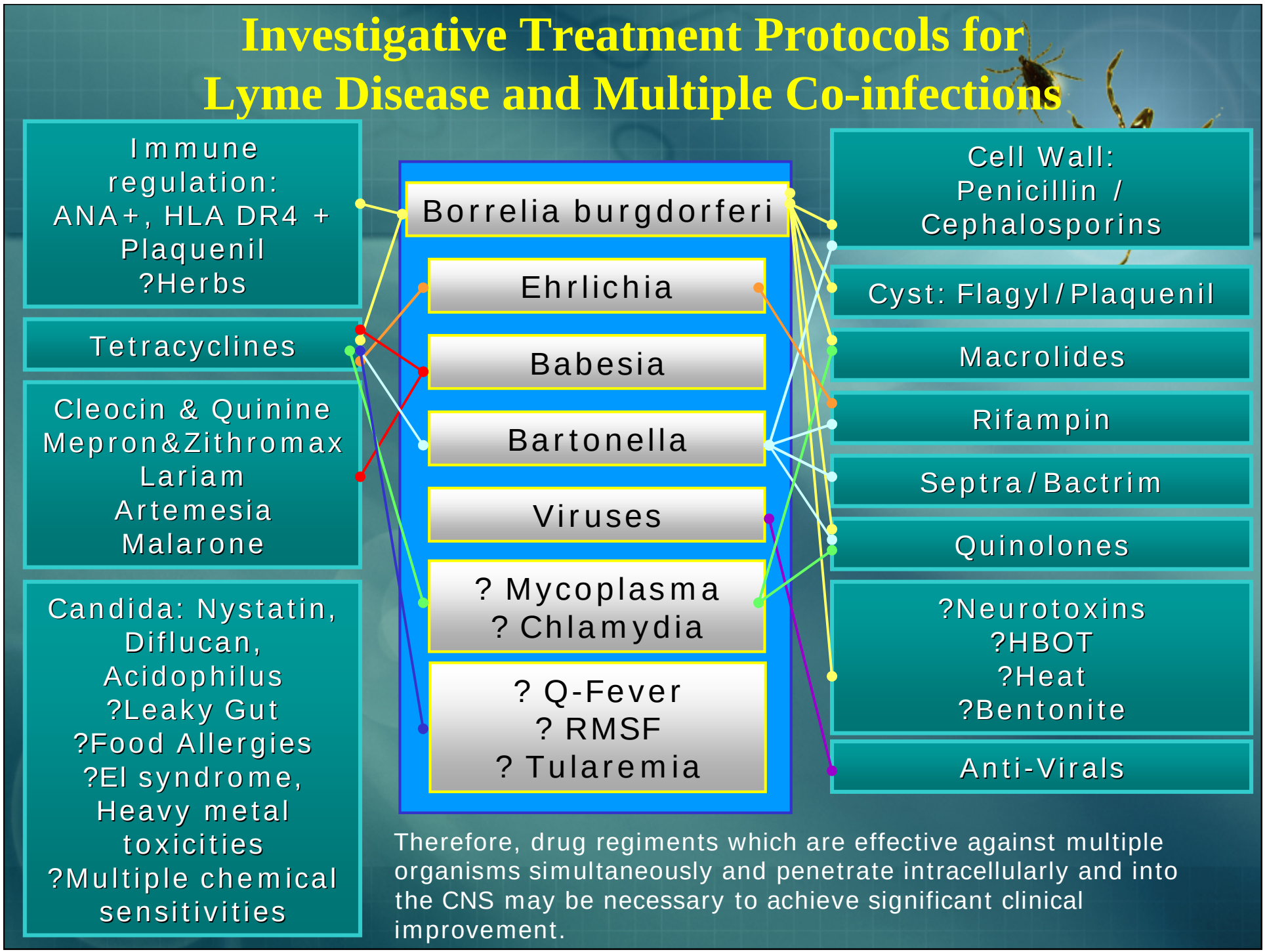
Treatment for Borrelia burgdorferi		
Cell Wall	Cystic Forms	Intracellular
PCN Amoxicillin Bicillin Cephalosporins Ceftin Cedax Omnicef IV Rocephin IV Claforan Other IV Vancomycin IV Primaxin	Plaquenil Flagyl Tinidazole	Macrolides Zithromax Biaxin Dynabac Quinolones Cipro Levaquin Avelox

Designing Combination Treatment Therapies

Lyme Disease	Bartonella	Babesia
•Amox+Probenecid+ Macrolide+Plaquenil •Bicillin+Macrolide+ Plaquenil •Cephalosporin (oral or IV) +Macrolide+ Plaquenil •Cell wall+ Plaquenil+ Macrolide+tetra	+ Septra	+Mepron +Malarone +Artemesia +Lariam
•Doxy+Plaquenil	+ Rifampin/or Quinolone	+Lariam +Malarone +Artemesia
•Macrolide+Plaquenil	+ Septra	+Mepron +Malarone +Artemesia +Lariam

- +/- Flagyl / Tinidazole (? pulsed)
- When mult. intracellular infx are present (Mycoplasma, Chlamydia), consider two intracellular

Investigative Treatment Protocols for Lyme Disease and Multiple Co-infections



Therefore, drug regiments which are effective against multiple organisms simultaneously and penetrate intracellularly and into the CNS may be necessary to achieve significant clinical improvement.

“Wisdom is the marriage of knowledge and experience bound by compassion.”

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