



# Lyme Disease: Question to the Board and Overview



Source: *Lancet Infectious Diseases* 2003 Aug; 3(8)

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RESEARCH – PREVENTION - HEALTH



# Question to the Board

- Review scientific evidence surrounding *Borrelia burgdorferi* infections
- Provide comments regarding the natural history, diagnosis, and treatment of Lyme Disease forms and stages
  - Known facts regarding chronic Lyme disease and current therapies
  - Gaps in current data and scientific knowledge

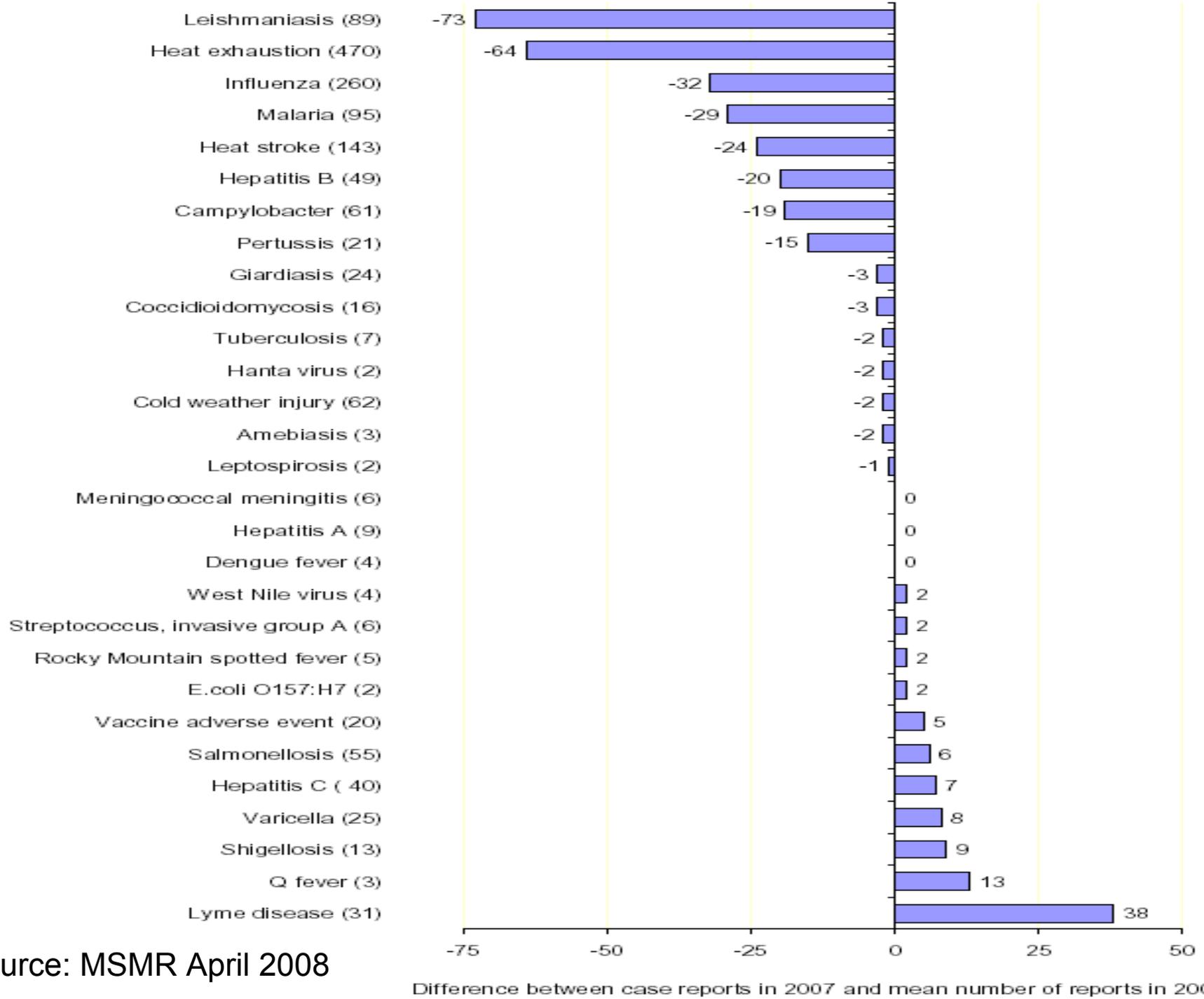


# Lyme Disease: Military Relevance

- Training and combat in endemic areas
  - Mean number of reports\* in 2004-2006: 31
  - Reports\* of LD events in 2007: 69
- \* Events reported by 07 April 2008 at US military medical treatment facilities, active component members, US Armed Forces

Figure 1. Number of reportable events among active component service members, US Armed Forces, in 2007 compared to the mean during 2004-2006

Reportable condition (mean number of reports in 2004-2006)



Source: MSMR April 2008



# Lyme Disease: Epidemiology

- Spirochaetal zoonotic tickborne disease
- Most common tick-borne disease in Northern Hemisphere
- Named after cluster of cases in Lyme and Old Lyme, CT, investigated by David Snydman and Allen Steere in 1976
- Agent: *Borrelia burgdorferi* (U.S.)
- Willy Burgdorfer isolated bacterium in 1982



Source: *The Journal of Clinical Investigation*;  
April 2004 113(8)



# Lyme Disease: Epidemiology (Continued)

- Hosts: white-tailed deer (adult ticks); small rodents, especially white-footed mice (larval & nymphal ticks)
- Vector: *Ixodes scapularis* (black-legged deer tick) - eastern North America
- Incubation Period in Humans: 3-32 days (mean 7-10 days)



Source: *Public Library of Science  
Biology* June 2006; 4(6)



# Lyme Disease: Case Distribution

- Endemic foci:
  - Atlantic Coast
  - Wisconsin
  - Minnesota
  - some areas of California & Oregon
- Northeast and Midwest:  
10-20% nymphal stage and 30-40% adult ticks infected with *B. burgdorferi*
- In contrast, *Ixodes pacificus* tick, the prominent vector on the West Coast, is a poor reservoir with 1-3% infected with *B. burgdorferi*

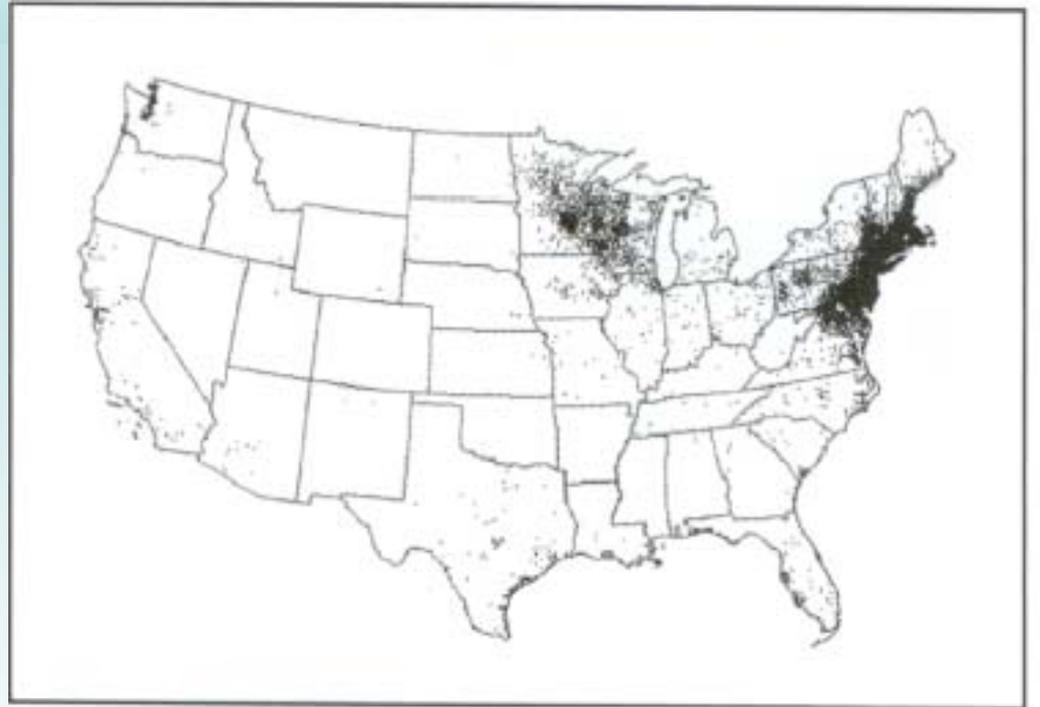


FIGURE 1. Reported cases of Lyme disease in the United States in 2005. Most cases were reported in New England (Connecticut, Rhode Island, New York, Pennsylvania, Delaware, New Jersey, Maryland, and Massachusetts) and in the Great Lakes region (Wisconsin and Minnesota). One dot is placed randomly within the county of residence for each reported case. From the Centers for Disease Control and Prevention.<sup>1</sup>



# Lyme Disease: Acute Stage

- Early symptoms intermittent and changing
- Illness typically begins in summer months

## **Early Systemic Manifestations (mean 7-10 days post-exposure):**

- 80% patients exhibit erythema migrans (EM) – single or multiple
- Malaise, fatigue, fever, headache, stiff neck, myalgia, migratory arthralgias and/or lymphadermopathy (may last several weeks in untreated patients)



# Clinical Signs



Source:[http://www.cdc.gov/ncidod/dvbid/lyme/ld\\_LymeDiseaseRashPhotos.htm](http://www.cdc.gov/ncidod/dvbid/lyme/ld_LymeDiseaseRashPhotos.htm)



# Lyme Disease: Acute Stage (Continued)

## Within Weeks – Months after EM Onset (may become chronic):

- Neurological abnormalities (Neuroborreliosis), cranial neuropathy (particularly unilateral or bilateral facial palsy) chorea, cerebellar ataxia, motor or sensory radiculoneuritis, myelitis, encephalitis with mentation difficulty, lymphocytic meningitis with episodic headache and mild neck stiffness
  - ❑ Approximately 15% untreated patients develop acute neuroborreliosis
- Carditis: arterioventricular block, acute myopericarditis or mild left ventricular dysfunction, and cardiomegaly (rare)
  - ❑ Approximately 5% untreated patients

Sources: *The Lancet Infectious Diseases* **2003**;3:489-500; *N Engl J Med* **2001**;345(2):115-125



# Lyme Disease: Chronic Stage

## Within Weeks-Years after EM Onset:

- Chronic neurological manifestations (chronic neuroborreliosis) – encephalopathy, polyneuropathy, leukoencephalitis
  - Up to 5% untreated patients
  - No inflammatory changes in CSF; however, intrathecal production of *B. burgdorferi* can often be demonstrated
  - Neither single-photon emission CT of the brain nor neuropsychological tests or memory have sufficient specificity to be helpful in diagnosis
- Optic nerve may be affected due to inflammation or increased intracranial pressure, especially in children, and may lead to blindness



# Lyme Disease: Chronic Stage (Continued)

## Within Weeks-Years after EM Onset:

- Intermittent episodes of swelling & pain in large joints, especially knees – may recur for several years and develop into chronic arthritis
  - ❑ About 60% untreated patients
  - ❑ Approximately 10% patients have persistent joint inflammation
  - ❑ Resistant Lyme arthritis is rare – may be result of cross-reactivity between OspA & human leukocyte function-associated antigen (hLFA-1) following natural infection with *B. burgdorferi*
  - ❑ *B. burgdorferi* DNA can be detected in PCR in synovial fluid (in up to 85% untreated patients) but cannot be cultured from joint fluids – culture negative
  - ❑ Patients with Lyme arthritis have higher borrelia-specific antibody titers than patients with any other manifestation of borreliosis

Sources: *The Lancet Infectious Diseases* 2003;3:489-500; *N Engl J Med* 2001;345(2):115-125



# Lyme Disease: Current and Potential Diagnostic Challenges

- Possibility of **reverting to different forms**: spheroblast-L-form variants or cysts
  - ❑ Controversial; *in vitro* assays indicate *B burgdorferi* may assume dormant state with cyst formation
  - ❑ Donta et al data showed treatment of patients with symptoms typical of chronic Lyme disease with macrolide antibiotics in addition to hydroxychloroquine (alkalinization) resulted in improved outcomes, since cysts are associated with low pH levels
- Challenges in **isolation of causative agent** at later stages:
  - ❑ Paucity of organisms in tissue samples of patients with extracutaneous manifestations
  - ❑ Dead spirochetes circulating in blood may give false positive results (PCR)
- Extremely **complex antigenic composition** of *B burgdorferi* and **unique genetic composition** including a linear chromosome and 21 linear and circular plasmids
  - ❑ Many structural proteins and immunodominant antigens encoded in plasmids
  - ❑ Ph & temperature variation in surface protein expression
  - ❑ Several important immunodominant antigens not expressed *in vitro* culture conditions and may be lost in culture
- Possibility of *B. burgdorferi* to engage in “**cloaking**” mechanisms
  - ❑ Binds to proteoglycan, collagen, plasminogen, integrin, and fibronectin *in vitro*
  - ❑ Can mask bacterium and make it invisible to immune system



# Lyme Disease: Diagnosis

- **Clinical Features**
  - ❑ Erythma Migrans (EM)
- **Common Laboratory tests – Limited Utility**
  - ❑ White blood cell count may be elevated or normal
  - ❑ Hemoglobin, hematocrit, creatinine, and urinalysis results usually normal
  - ❑ If neurologic involvement present – CSF samples show moderate lymphocytic pleocytosis, elevated protein concentrations, and normal to slightly low glucose concentrations
- **Direct Detection of Antigens – Limited Utility**
  - ❑ No gold standard for CSF samples
  - ❑ PCR for chromosomal and plasmid genes: most sensitive from EM skin samples (64% sensitivity) and synovial fluid with OspA primers (85% patients with Lyme arthritis); blood samples (10-18% sensitivity); CSF samples (38% early NB, 25% late NB)
  - ❑ Not commonly recommended for routine diagnosis: possibility of dead spirochetes circulating in bloodstream may give false positive



# Lyme Disease: Diagnosis (Continued)

- **2-Tier Serological Tests – CDC Guidelines**

- Controversy surrounds the test with regard to using it as a diagnostic tool, since it is population-based instead of clinically based, and sensitivity is questioned

## 1. ELISA

- Insensitive during first weeks of infection
- False positives can occur with mononucleosis, autoimmune states, and *Treponema pallidum* infection
- May remain negative in people treated early with antibiotics

## 2. IgG and IgM Western Immunoblot (IB) on those samples testing reactive or indeterminate

- More specific, but sensitivity depends on timing of test
- IgM IB criteria to be used at no more than 4 weeks LB duration and IgG IB at any stage of LB



# Lyme Disease: Diagnosis (Continued)

- **Few studies have published on the evaluation of two-tier testing**
- **Evaluation of CDC Guideline – Study by Bacon et al (2003):**
  - ❑ Sensitivity was 38% on sera from patients with EM during acute phase and 67% during their convalescence
  - ❑ Sensitivity increased to 87% on sera from patients with early neuroborreliosis and 97% in sera from patients with Lyme arthritis
- **Peptide and recombinant assays - C6 peptide:**
  - ❑ high immunogenicity, high specificity
  - ❑ cross-reactive among the different *B burgdorferi* genospecies causing Lyme disease in different geographical areas
  - ❑ Replaced IB in second-tier test in Europe (commercial assay, not approved in US)
  - ❑ Study by Steere et al (2008) found C6 peptide ELISA was sensitive to support diagnosis of Lyme disease but two-tier testing was associated with slightly better specificity

Sources: *J Infect Dis* **2003**;187:1187-99; *Infect Dis Clin N Am* **2008**;22:301-313; *Clin Infect Dis* **2008**;47:188-95



# Lyme Disease: Treatment- IDSA Guidelines

## Early Localized Disease:

- Doxycycline (Vibramycin), 100 mg orally 2x daily 14-21 days
- Alternative: cefuroxime axetil (Ceftin), 500 mg orally 2x daily

## Neurologic Abnormalities (early or late):

- Ceftriaxone 2 g IV, 1x daily 14-28 days
- Cefotaxime 2 g IV every 8h 14-28 days
- Penicillin G 3.3 million U IV every 4h 14-28 days
- Alternative: Doxycycline (Vibramycin), 100 mg orally 3x daily 30 days
- **Facial Palsy Alone:** oral regimens may be adequate



# Lyme Disease: Treatment - IDSA Guidelines (Continued)

## **Arthritis (intermittent or chronic):**

- Oral doxycyclin regimens for 30-60 days or ceftriaxone IV regimens for 14-28 days

## **Cardiac Abnormalities:**

- First degree arterioventricular block: oral doxycyclin regimens for 14-21 days
- Higher degree arterioventricular block (PR interval > 0.3 sec): ceftriaxone IV regimens and cardiac monitoring

## **Pregnant Women:**

- Standard therapy; avoid doxycyclin



# “Chronic Lyme Disease”

- Also referred as “post Lyme disease syndrome”
- **No accepted definition or diagnostic criteria** exist
- **Heterogeneous** patient population
- Small percentage of patients (after appropriate treatment) continue to **experience subjective symptoms**: musculoskeletal pain, neurocognitive difficulties, fatigue, and “neuropsychiatric” symptoms
- May last for years
- Similarities to chronic fatigue syndrome and fibromyalgia
- Have **no evidence of past or current infection** with *B.burgdorferi*
- Most frequent in patients whose symptoms suggestive of early dissemination of *B.burgdorferi* to nervous system, delayed treatment

Sources: *The Lancet Infectious Diseases* **2003**;3:489-500; *Mayo Clin Proc* **2008**;83(5):566-571;



# “The Lyme Wars”

- Prolonged symptoms are result of **slowly resolving inflammation** in treated patients or **chronic fatigue syndrome** versus a **persistent infection** where agent difficult or impossible to eradicate
- Treat patients **symptomatically** or with **prolonged** courses of **antibiotic therapy**

Sources: *Mayo Clin Proc* **2008**;83(5):566-571; *Neurology* **2007**;69(1):91-102; *Int J Med Microbiol* **2002**;291:125-137



# “The Lyme Wars” (Continued)

## Some Arguments and Counter-Arguments Used:

- ❑ **Apparent similarity with symptoms** experienced by untreated or partially treated Lyme disease
  - IDSA states post-treatment symptoms appear to have similar prevalence in general US population and must be evaluated in the context of “background” complaints
  
- ❑ Long-term antibiotic therapy has benefitted some patients experiencing post-treatment symptoms
  - IDSA claims substantial placebo effect occurred in study patient populations
  - Patients in trials reporting cognitive difficulties had normal baseline neuropsychological test scores
  
- ❑ Agent believed to overcome presence of  $\beta$ -lactams by **forming spheroblast-L-form variants or cysts**
  - IDSA claims *in vitro* data does not have clinical significance

Sources: *Mayo Clin Proc* **2008**;83(5):566-571; *Neurology* **2007**;69(1):91-102; *Int J Med Microbiol* **2002**;291:125-137; *Arthritis & Rheumatism* **2007**;56(4):1325-1335; *Clin Infect Dis* **2007**;45(2):145-57; *Infect Dis Clin N Am* **2008**;22:341-360; *Clin Infect Dis* **2006**;43:1089-1134



# “The Lyme Wars” (Continued)

- ❑ **Agent possesses ability to invade and survive** in human endothelial cells *in vitro* and has been observed in experimentally-infected murine cardiac myocytes
  - IDSA claims *in vitro* data does not have clinical significance
  
- ❑ Antibodies can also persist for months or years after an infection = serologic **tests do not accurately distinguish past from active infection**
  
- ❑ **Lack of objective evidence** of *B. burgdorferi* infection using PCR or culture

Sources: *Mayo Clin Proc* **2008**;83(5):566-571; *Neurology* **2007**;69(1):91-102; *Int J Med Microbiol* **2002**;291:125-137; *Arthritis & Rheumatism* **2007**;56(4):1325-1335; *Clin Infect Dis* **2007**;45(2):145-57; *Infect Dis Clin N Am* **2008**;22:341-360; *Clin Infect Dis* **2006**;43:1089-1134



# Selected Studies: Prolonged Antibiotic Treatment

## Published Prospective Placebo-Controlled Trials of Prolonged Antibiotic Treatment:

- **Klempner MS et al. *N Engl J Med* 2001; 345:85-92**
  - ❑ Found no significant difference between treatment with IV and oral antibiotics for 90 days and placebo
- **Krupp LB et al. *Neurology* 2003; 60:1923-30**
  - ❑ Stated no improvement in cognitive function (reaction time test)
- **Wormser GP et al. *Ann Intern Med* 2003; 138:697-704**
  - ❑ Observed no significant differences in neurocognitive testing between patients with early Lyme disease
- **Fallon BA et al. *Neurology* 2008;70(13):992-1003**
  - ❑ Found short-term cognitive improvement for patients with posttreatment Lyme encephalopathy; relapse in cognition occurs after antibiotic discontinued

## Published Data on Impact of Long-Term Antibiotic Therapy:

- **Donta ST *Clin Infect Dis* 1997; 25(Suppl 1):S52-6**
  - ❑ Demonstrated correlation between longer treatment time and improvement or cure among patients
- **Kaplan RF et al *Neurology* 2003; 60:1916-22**
  - ❑ Observed no difference in therapy benefit between additional antibiotic therapy and placebo
  - ❑ Found patients with post-treatment chronic Lyme disease with symptoms, but no evidence of persisting infection also do not show objective evidence of cognitive impairment



# Lyme Disease Treatment Guideline Comparison – IDSA and ILADS

- **The International Lyme and Associated Diseases Society (ILADS)**  
“Evidence-Based Guidelines for the Management of Lyme Disease”  
November 2006
  - ❑ Called for retraction of the IDSA Lyme Treatment Guidelines
  - ❑ Suggest more aggressive treatment for people at risk, including treatment for symptomatic presentations, longer courses of antibiotic treatment, repeat antibiotics for recurrence, early use of antibiotics, and that treatment should not be withheld based on laboratory testing
- **Infectious Diseases Society of America (IDSA) Guidelines:**
  - ❑ Clinicians should consider waiting several months before initiating retreatment for cases of Lyme arthritis with antimicrobial agents because of anticipated slow resolution of inflammation after treatment
  - ❑ Symptomatic treatment is recommended for patients with no resolution of symptoms
  - ❑ Because of a lack of biologic plausibility, efficacy, absence of supporting data, or potential for harm, long-term antibiotic therapy is not recommended

Sources: *Clin Infect Dis* **2006**;43:1089-1134; *Expert Rev Anti-Infect Ther* **2004**;2(1):S1-S13



# Lyme Disease: Gaps and Areas For Further Research

- Further randomized, double-blind placebo-controlled trials of prolonged antibiotic therapy needed
- Use past studies to guide hypotheses and further research with stronger study designs
- Improve diagnostic capabilities for later stages of disease
- Standardization of case definition for chronic Lyme disease (post-Lyme disease syndrome)
- Further research needed to understand possible mechanisms and pathophysiology of chronic symptoms following Lyme disease
  - ❑ Immune mediation/modulation may be a component
- Further research needed to find effective therapies for chronic symptoms following Lyme disease
  - ❑ Issue may be to unbundle therapy from the diagnosis



# Question to the Board

- Review scientific evidence surrounding *Borrelia burgdorferi* infections
- Provide comments regarding the natural history, diagnosis, and treatment of Lyme Disease forms and stages
  - Known facts regarding chronic Lyme disease and current therapies
  - Gaps in current data and scientific knowledge



# Backup Slides



# Lyme Disease: Vaccines

- **LYMErix Vaccine (SmithKline Beecham Biologicals, Philadelphia, PA)**
  - Recombinant vaccine directed toward lipoprotein outer surface protein A (OspA)
    - ❑ Antibodies against Osp A are borreliacidal & seen in sera of patients with late-stage LB (Fikrig et al 1990)
  - Developed in 1998
  - Recommended for selected people at increased risk for Lyme disease
  - Available until March 2002
    - ❑ Efficacy reported as 76%
    - ❑ Low demand, high price, possible association with development of autoimmune arthritis or Lyme disease (although evidence to support such claims was insufficient)
  - Class-action lawsuit
- New vaccines forthcoming

Sources: *N Eng J Med* **1998**;339: 209-15; *Mayo Clin Proc* **2008**;83(5):566-571; *Can J Infect Dis* **2000**;11(3):132-133; *Science* **1990**;250:553-6