


Challenge to 'Implausibility' of Persistent *B. burgdorferi* Infection--Contesting the Underlying Basis for Treatment Limitations for Early and Late Lyme Disease and Post-Lyme Syndrome

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Challenge to the following statement from 2006 IDSA Guidelines (p. 1118):

“The notion that symptomatic, chronic B. burgdorferi infection can exist despite recommended treatment courses of antibiotics (tables 2 and 3) in the absence of objective clinical signs of disease, is highly implausible as evidenced by (1) the lack of antibiotic resistance in this genus [39, 40, 310], (2) the lack of correlation of persistent symptoms with laboratory evidence of inflammation or with the eventual development of objective physical signs [223, 257, 288, 289], and (3) the lack of precedent for such a phenomenon in other spirochetal infections [315–317]. Additional compelling evidence against the hypothesis that persistent symptoms are the result of persistent infection is the fact that the concentrations of antibodies against B. burgdorferi in many of these patients diminish to undetectable levels [257, 286, 288, 318]. The panel is unaware of any chronic infection in which antibody titers diminish despite persistence of the causative organism. In syphilis, patients who are regarded as having treatment failure typically have persistent or rising titers of antibodies [319]. Finally, Lyme disease lacks characteristics of other infections that justify longer treatment courses, such as infections in immunodeficient hosts, infections in which a pathogen is inhibited but not killed by antimicrobial therapy or in which available antimicrobials are minimally active in vitro, infections caused by an intracellular pathogen, infections involving a biofilm, infections on a heart valve, or infections involving a clinical site in which there is ischemia, a foreign body, a sequestrum, or frank pus [170]. The ‘cystic’ forms of B. burgdorferi that have been seen under certain growth conditions in vitro have not been shown to have any clinical significance [320].” (NO EVIDENCE RATING)

This challenge is based on  Stricker RB. Counterpoint: Long-term antibiotic therapy improves persistent symptoms associated with Lyme disease. Clin Infect Dis. 2007 Jul 15;45(2):149-57.

B. burgdorferi is a complex bacterium [1, 2]. It has >1500 gene sequences with at least 132 functioning genes. In contrast, *Treponema pallidum*, the spirochetal agent of syphilis, has only 22 functioning genes. The genetic makeup of *B. burgdorferi* is quite unusual. It has a linear chromosome and 21 plasmids, which are extrachromosomal strands of DNA. This is 3 times more plasmids than any other known bacteria (*Chlamydia* comes in a distant second, with 7 plasmids). Plasmids are thought to give bacteria a kind of “rapid response” system that allows them to adapt very rapidly to changes in the environment, and the complex genetic structure of *B. burgdorferi* suggests that this is a highly adaptable organism [1, 2]. In addition to its complex genetic makeup, *B. burgdorferi* engages in so-called “stealth pathology” to evade the human immune response [3–42].

Stealth pathology involves 4 basic strategies: immunosuppression; genetic, phase, and antigenic variation; physical seclusion; and secreted factors (table 1). These strategies are outlined below.

Table 1. “Stealth” pathology of *Borrelia burgdorferi*.

Immunosuppression

Tick saliva components
Complement inhibition
Inhibitory cytokine induction (IL-10)
Lymphocyte/monocyte tolerization
Antibody sequestration in immune complexes

Genetic, phase, and antigenic variation

Gene switching (trypanosomes)
Mutation/recombination (HIV)
Variable antigen expression (*Neisseria* species)
Dormant state, autoinduction (*Mycobacterium* species)
Fibronectin binding (*Staphylococcus* and *Streptococcus* species)

Physical seclusion

Intracellular sites

Multiple cell types (synovial cells, endothelial cells, fibroblasts, macrophages, Kupffer cells, and nerve cells)
Persistent infection in vitro (8 weeks)

Extracellular sites

Privileged sites (joints, eyes, and CNS)
Cloaking mechanisms (binding to proteoglycan, collagen, plasminogen, integrin, and fibronectin)

Secreted factors

Hemolysin (BlyB)
Porin (Oms 28)
Adhesin (Bgp)
Pheromones (DPD/AI-2)
Aggrecanase (ADAMTS-4)

IMMUNOSUPPRESSION

During a tick bite and before transmission of the Lyme spirochete, tick saliva containing analgesic, anticoagulant, and immunosuppressive factors is expressed into the wound, allowing the spirochete to penetrate the skin and evade the local immune response [3–5]. *B. burgdorferi* also induces immunosuppression by complement inhibition and induction of inhibitory cytokines, such as IL-10. In addition, the bacterium induces monocyte and lymphocyte tolerization and antibody sequestration in immune complexes—all mechanisms of evading the immune response [6–11].

GENETIC, PHASE, AND ANTIGENIC VARIATION

B. burgdorferi engages in genetic, phase, and antigenic variation that shares various features with other organisms [12–15]. For example, gene switching is similar to what is seen with trypanosomes, mutation and recombination are typical of HIV, variable antigen expression is seen with *Neisseria* species, autoinduction of dormant organisms occurs in mycobacterial infection, and fibronectin binding occurs with staphylococcal and streptococcal infection. *B. burgdorferi* may assume a dormant state with cyst formation [16–21]. Although spirochetal persistence in the cyst form is a controversial issue, it has recently been shown that neutrophil calprotectin can induce a dormant state in the spirochete, allowing it to persist in tissue without replicating and providing the means to avoid antibiotics [22]. Although antibiotic resistance associated with gene mutation was previously thought to be rare in *B. burgdorferi* infection [23], recent studies have demonstrated gene mutations in the Lyme spirochete that confer in vitro resistance to various antibiotics [24, 25]. The clinical implication of these gene mutations is uncertain at present.

PHYSICAL SECLUSION

The Lyme spirochete uses physical seclusion at intracellular sites as a means of evading the immune response in multiple cell types, including synovial cells, endothelial cells, fibroblasts, macrophages, Kupffer cells, and neuronal cells [26–35]. In culture, *B. burgdorferi* can be grown in fibroblasts for 18 weeks, suggesting that the organism can thrive over long periods of time in the right place and under the right conditions. Physical seclusion at extracellular sites, including the joints, eyes, and CNS, may also promote survival of the Lyme spirochete. In addition, *B. burgdorferi* engages in “cloaking” mechanisms by binding to proteoglycan, collagen, plasminogen, integrin, and fibronectin. These substances can mask the bacterium and make it invisible to the immune system [30–34].

SECRETED FACTORS

There are a number of factors that are secreted either by *B. burgdorferi* itself or in response to infection with the spirochete [36–43]. For a number of years, it has been known that *B. burgdorferi* secretes a hemolysin, although its function is uncertain [36]. More recently, the spirochete has been shown to elaborate porin and adhesin, 2 proteins that allow bacteria to adhere to cells and pierce the cell wall to gain entry [37]. Even more recently, *B. burgdorferi* was found to secrete pheromones, including AI-2, which is also secreted by mycobacteria [38–42]. This is the first time that a spirochete has been shown to secrete an autoinducer and suggests that the Lyme spirochete engages

in autoresuscitation like other dormant organisms, such as the tubercle bacillus [38–42]. In addition, *B. burgdorferi* can induce secretion of aggrecanase, an enzyme that damages cartilage [43]. This may be a mechanism by which the bacterium induces damage and inflammation in joints.

Armed with these weapons of “stealth pathology,” the Lyme spirochete is a formidable infectious agent, and it is not only completely plausible but also highly likely that this organism causes chronic, persistent infection when Lyme disease is untreated or undertreated. Thus the IDSA guidelines contention that persistent infection with *B. burgdorferi* is ‘highly implausible’ should be rejected.

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