Basic science (mostly) Lyme/Borrelia references referring to chronic or persistent infection/disease

Howe Mayer Barbour (NIAID, Rocky Mountain Labs) **A single recombinant plasmid expressing two major outer surface proteins of Lyme disease spirochete Science 1985;227:645-5**
https://www.ncbi.nlm.nih.gov/pubmed/3969554

The **chronicity** of some of the manifestations of Lyme disease, such as the oligoarticular arthritis and meningoradiculitis, suggests that the **host cannot effectively rid itself of the infecting agent**. Alternatively, the host's immune response to the spirochete may actually induce or accentuate the pathological lesions associated with this disorder. Thus, knowledge of the balance struck between the host's immune system and the spirochete during **chronic** infection may be a key to understanding the pathogenesis of Lyme disease.

Johnson, Kodner, Russell In vitro and in vivo susceptibility of Lyme disease spirochete, *B burgdorferi,* to four antimicrobial agents Antimicrob Agents Chemother 1987:
https://www.ncbi.nlm.nih.gov/pubmed/3566246

These observations are particularly important, since the **chronic** forms of Lyme disease and related disorders appear to be due to the **persistence** of *B. burgdorferi* in the affected sites (4,17,19,26,27).

Johnson, Russell - US Patent 4,721,617 - Vaccine against Lyme disease January 26, 1998:

...The **chronic** forms of the disease such as arthritis (joint involvement), acrodermatitis chronica atrophicans (skin involvement), and Bannwart's [sic] syndrome (neurological involvement) may last for months to years are are associated with the persistence of the spirochete...

The infection may be treated at any time with antibiotics such as penicillin, erythromycin, tetracycline, and ceftriaxone. Once infection has occurred, however. the drugs may not purge the host of the spirochete but may only act to control the **chronic** forms of the disease. Complications such as arthritis and fatigue may continue for several years after diagnosis and treatment.

Dattwyler, Volkman, Halperin, Luft, Thomas, Golightly. Specific immune responses in Lyme borreliosis: Characterization of T and B cell responses to *Borrelia burgdorferi* Ann NY Acad Sci 1988:
https://www.ncbi.nlm.nih.gov/pubmed/3263829

Lyme borreliosis, *B burgdorferi* infection, is a **chronic progressive** infection involving multiple organ systems including the skin, the central and peripheral nervous systems, the heart, liver, and kidney, and the musculoskeletal system (1-3). As in other **chronic** infectious diseases, host responses to this infecting microorganism play a major role in shaping the clinical expression of this **persistent** spirochetosis.

As with any infection, the immune response plays a pivotal role in the containment of the invading microorganism. In any **chronic** infection, the microbe must evolve strategies to avoid eradication by the host. Such strategies include suppression of the host's defenses; evasion of host defenses through antigenic mimicry or antigenic variation; or invasion of immunologically privileged sites...

Erythema chronicum migrans (ECM) has classically been the best marker of Lyme borreliosis.

Bergstrom (Sweden) **Bundoc Barbour** (U TX San Antonio)**, Molecular analysis of linear plasmid-encoded major surface proteins, OspA and OspB, of the Lyme disease spirochaete *Borrelia burgdorferi* Molecular Microbiology 1989:**
https://www.ncbi.nlm.nih.gov/pubmed/2761388

"In many patients the infection of some tissues, particularly the brain and joints, persists for years and can be severely disabling. These forms of **chronic** Lyme borreliosis are a consequence of the host's inability to rid itself of the infecting agent and are perhaps also caused by the development of an autoimmune immunological reaction (Steere et al, 1979)."

Aberer, Brunner, Suchanek, Klade, Barbour (UT San Antonio)**, Stanek, Lassmann** (Univ Vienna) **Molecular mimicry and Lyme borreliosis: A shared antigenic determinant between *Borrelia burgdorferi* and human tissue Ann Neuro 1989:**
https://www.ncbi.nlm.nih.gov/pubmed/2481425

By testing monoclonal antibodies directed against various borrelia antigens, we found an antigenic determinant shared by the 41 kDa flagella protein and human tissue, especially prominent on myelinated fibers of human peripheral nerve, on nerve cells and axons of the central nervous system, as well as on certain epithelial cells (including joint synovia) and on heart muscle cells. Immune reactions against such a shared antigen could play a pathogenic role in **chronic** organ manifestations of Lyme borreliosis.

... Besides the various neurological diseases and Lyme arthritis, fatal respiratory distress syndrome (6), hepatitis (5), endomyopericarditis (7) and interstitial nephritis (4) have been described. However, if autoimmune reactions are important for these alterations, additional factors, such as local antigen presentation and histocompatibility antigen expression, must also be involved because the **chronic** manifestations in Lyme borreliosis are so variable.

Luft Gorevic Halperin Volkman Dattwyler A perspective on the treatment of Lyme borreliosis Rev Infect Dis 1989 Sep-Oct; 11 Suppl 6:
https://www.ncbi.nlm.nih.gov/pubmed/2682965

Abstract
...Clinical studies have documented the efficacy of antibiotics, but therapy has failed in as many as 50% of cases of **chronic** infection..

Persistent *B burgdorferi* infection can produce various insidious and **chronic** dermatologic, neurologic, and rheumatologic manifestations [3-15]. The pathophysiologic mechanisms involved in the **chronic** phase of this illness remain incompletely defined, It has not been determined whether persistent symptoms are secondary to some immunologic process or whether anything short of total eradication of *B burgdorferi* is sufficient for ultimate cure and resolution of symptoms.

Dattwyler Volkman Luft Immunologic aspects of Lyme borreliosis Rev Infect Dis 1989 Sep-Oct; 11, Suppl 6:

https://www.ncbi.nlm.nih.gov/pubmed/2682961

As in any **chronic** infectious disease, host responses are thought to play a major role in shaping the clinical expression of this illness. These responses include and early and vigorous T cell response to the presence of the Lyme spirochete and a more slowly evolving B cell response (16,17).

The failure of early antimicrobial therapy to completely eradicate the infection and the subsequent development of a **chronic** illness make this disease especially difficult to diagnose in patients who do not develop a mature antibody response. However, specific T cell and/or local humoral responses may be demonstrable in patients who lack diagnostic levels of circulating antibodies to *B burgdorferi* (17,24-26).

Dattwyler Luft Antibiotic treatment of Lyme borreliosis Biomed & Pharmacother 1989:

https://www.ncbi.nlm.nih.gov/pubmed/2686769

It is now recognized that only by understanding the different lines of investigation in Europe and the US can we achieve a true appreciation of the multiplicity of acute and **chronic** disease manifestations due to *B burgdorferi* infection.

If not effectively treated during the local or the acute disseminated phase of infection, a **chronic** phase of infection can develop. Clinical manifestations observed during this **chronic** phase include **chronic** meningitis, meningoradiculitis, encephalitis, peripheral neuropathy, lymphocytoma, ACA and arthritis

It is now well recognized that late neurological disorders are common in *B burgdorferi* infection, that CNS infection can be documented by demonstrating intrathecal anti- *B burgdorferi* antibody production, and that CNS infection is frequently associated with **chronic** headache and a profound sense of fatigue which may indicate a **chronic** encephalopathic state.

Duray Histopathology of clinical phases of human Lyme disease Rheum Dis Clin North Am 1989:

https://www.ncbi.nlm.nih.gov/pubmed/2685926

Lyme borreliosis in humans can be divided into acute, subacute and **chronic** states of inflammation with variable degrees of dysfunction. (15, 31-34). Multisystem involvement appears to be random and unpredictable, with **chronic** states of **persistence** in some cases.

Chronic Lyme borreliosis
A subset of patients go on to **chronic, persistent** disease in the presence of continuing spirochetes in selected sites with continuing inflammation and humoral immunologic reactions. These manifestations are not inevitable because the disease process may be completed at the end of each prior phase of the inflammatory illness, and not progress any further. However, **chronic** Lyme borrelial disease occurs worldwide predilecting for the skin and central and peripheral nervous systems in Europe, (6,9) and in the muscular skeletal system, particularly the joints and synovium, in North America (29, 53). This target organ selectivity in either hemisphere in **chronic** disease is a phenomenon not well understood but may relate to minor differences in the North American versus the European strains of *B burgdorferi*.

Chronic Cutaneous Involvement
The skin is involved in **chronic** disease as a consequence of the continuing presence of the spirochete in deep dermal and subcutaneous tissues. This may take place over a period ranging from many months to several years.

Acrodermatitis **Chronica** Atrophicans (ACA)
ACA is a peculiar, **chronic**, long-term Lyme dermatosis defined clinically as a purple, red-rubor discoloration of the skin, generally of the acral limbs, hands, wrists, forearms, elbows, or ankles and lower legs...

Speculation of the Histopathogenesis
...With continuing infection, demyelination is thought to occur in some humans. Demyelination may result from immunologic cross reactivity directed against variable major protein in a given infection. Regardless, demyelination does seem to be fundamental to many of the neurologic manifestations in **chronic** Lyme neural infections.

Brandt Riley Radolf Norgard Immunogenic integral membrane proteins of *B burgdorferi* are lipoproteins Infect Immun 1990:

https://www.ncbi.nlm.nih.gov/pubmed/2318538

Lyme disease, a tick-borne infection caused by the spirochete *Borrelia burgdorferi*, is a **chronic** disorder characterized by dermatologic, rheumatologic, cardiac, and neurological manifestations.

...While differences between these infections and between their causative organisms undoubtedly exists, it is plausible that *B burgdorferi* and *T pallidum* share some parasitic strategies and that common host immune mechanisms are operative in the containment of both **chronic** diseases.

Wallich Moter Simon Ebnet Heiberger Kramer The *Borrelia burgdorferi* flagellum-associated 41-kilodalton antigen (flagellin): Molecular cloning, expression and amplification of the gene Infect Immun 1990:

https://www.ncbi.nlm.nih.gov/pubmed/2341173

In humans Lyme disease appears as a **chronic progressive** disease that involves multiple organs, including the heart, the liver, the kidneys, the musculoskeletal system, the skin, and the central and peripheral nervous systems.

Ma Sturrock Weis Intracellular localization of *B burgdorferi* within human endothelial cells Infect Immun 1991:

https://www.ncbi.nlm.nih.gov/pubmed/1987083

The demonstration of *Bb* within endothelial cells suggests that intracellular localization may be a potential mechanism by which the organism escapes from the immune response of the host and may contribute to **persistence** of the organism during the later stages of Lyme disease.

Szczepanski Benach Lyme borreliosis: Host responses to *Borrelia burgdorferi* Microbiol Rev 1991:

https://www.ncbi.nlm.nih.gov/pubmed/2030671

...This multisystemic and **chronic** tick-borne spirochetosis is of world-wide distribution and has been the subject of various mongraphs (18,66,113,121) and recent reviews (5,47,114)... In this article, we will focus on studies investigating interactions between the spirochetes and the host. In so doing, we will attempt to present current hypotheses of how the disease progresses and to indicate the directions for future investigations into the **chronic** nature of Lyme disease.

...How do spirochetes evade the immune response? Is the **chronic** condition in Lyme disease the result of antigenic variability such as is seen in the relapsing fever borrelia (8,9), or is the **chronic** condition associated with persistent antigen perpetuated by a specific immune response to the spirochete? Does an autoreactive condition arise as a result of molecular mimicry between the bacterium and host. leading to a continuous cycle of injury in the patient?

Coleman Benach Characterization of antigenic determinants of *Borrelia burgdorferi* shared by other bacteria JID 1992:

https://www.ncbi.nlm.nih.gov/pubmed/1372635

“Lyme disease is a **chronic**, multisystem disorder involving the skin, nervous system, joints and heart [1]”

“The B cell response in Lyme disease is characterized by the early recognition of a limited number of antigens. In the **chronic** phase of the disease, a much larger repertoire of antigens is recognized (5,6)”

Bergstrom Garon Barbour MacDougall Extrachromosomal elements of spirochetes Res Microbiol 1992:

https://www.ncbi.nlm.nih.gov/pubmed/1475522

...During Lyme borreliosis, caused by *B. burgdorferi*, **chronic** infection is often established. In Lyme borreliosis, this is characterized by an **inability of the immune system to clear the infection**. Perhaps this is a means by which *B. burgdorferi* increases its probability of transmission to new hosts...

Dorward Huguenel Davis Garon Interactions between extracellular *Borrelia burgdorferi* proteins and non-*Borrelia*-directed Immunoglobulin M antibodies Infect Immun 1992:
https://www.ncbi.nlm.nih.gov/pubmed/1541558

Infection with the spirochete *B burgdorferi* causes the acute and **chronic** manifestations of Lyme borreliosis. Despite considerable work on humoral and cell-mediated responses to infection, which has recently been reviewed, the pathogenic mechanisms that contribute to **chronic** disease induced by this spirochete remain obscure... However, the **persistent** infections documented in humans and animal models indicate that **immune clearance is either rare or nonexistent** (24,25)

24 = Steere Lyme disease NEJM 1989
25 = Szczepanski Benach Lyme borreliosis Host responses to *B burgdorferi* Microbiol Rev 1991

Luft Mudri Jiang Dattwyler Gorevic Fischer Munoz Dunn Schubach The 93-kilodalton protein of *Borrelia burgdorferi* An immunodominant protoplasmic cylinder antigen Infect Immun 1992:
https://www.ncbi.nlm.nih.gov/pubmed/1398941

In many untreated cases, the acute infection is self limiting and becomes latent only to recrudesce later in life as a **chronic** infection involving the joints, heart, nervous system, or skin. The symptoms associated with the **chronic** infection may be vague and not associated with demonstrable clinical signs of disease. It is unclear whether the vague symptoms of late disease can be attributed to an actual ongoing infection or whether they result from some other pathogenic mechanism.

... patients with evidence of **chronic** infection have been reported to have negative serum antibody titers (23,35,41,72).

Montgomery Nathanson Malawista The fate of *Borrelia burgdorferi,* the agent for Lyme disease, in mouse macrophages. Destruction, survival, recovery J Immunol 1993:
https://www.ncbi.nlm.nih.gov/pubmed/8423346

Abstract
...Persistence of spirochetes within macrophages provides a possible pathogenetic mechanism for **chronic** or recurrent Lyme disease in man.

... Although most patients are cured by antibiotic therapy, Lyme disease may sometimes progress or recur despite therapy, perhaps because spirochetes survive in privileged sites away from the immune system or antibiotic, such as the central nervous system or inside cells.

Although spirochetes become more difficult to find as Lyme disease progresses in vivo, there is reason to believe that they are driving the illness throughout its course. Evidence in favor of a reservoir of live spirochetes includes the frequent response of late symptoms to antibiotics, the enlarging antigen specificity of immune sera from patients in later stages of disease, suggesting newly exposed spirochetal

epitopes (2), and the occasional identification of spirochetes in affected areas (3,4). Inasmuch as the macrophage acts as a reservoir for numerous other infectious agents, we investigated whether it might serve a similar role in Lyme disease.

Discussion
... Our results show that *B burgdorferi* can survive via a route that is distinct kinetically from its prominent pathway of degradation, and that such organisms retain the ability to multiply...

Barbour Fish The biological and social phenomenon of Lyme disease Science 1993:

https://www.ncbi.nlm.nih.gov/pubmed/8503006

Late Lyme disease is not likely to show a clear improvement within the time frame of the therapy, at least not for the standardly recommended period. Not surprisingly, there is controversy about whether the appropriate treatment duration for **chronic** Lyme disease is measured in weeks or months (5, 68, 78).

Golightly Laboratory considerations in diagnosis and management of Lyme borreliosis J Clin Path 1993:

https://www.ncbi.nlm.nih.gov/pubmed/8438790

When clinical findings are consistent with late or **chronic** disease (e.g. arthritis) a negative result militates against the diagnosis. **Chronic** Lyme disease samples are generally positive in high titer)13,46). This may be true even in the case of recently treated patients because titers may remain positive for years despite successful treatment. Nevertheless, there are exception, and negative, low, or decreasing titers, although uncommon in untreated **chronic** Lyme disease, may occur. (46-48).

Fikrig Bockenstedt Barthold Chen Ali-Salaam Telford Flavell Sera from patients with chronic Lyme disease protect mice from Lyme borreliosis JID 1994:

https://www.ncbi.nlm.nih.gov/pubmed/8158028

“These studies show that some humans **chronically** infected with *B. burgdorferi* produce protective antibodies. Our data showing that sera from patients with late- but not early-stage Lyme disease can partly protect mice from infection correlates with our clinical observations. In general, patients with **chronic** Lyme disease do not develop new episodes of erythema migrans (unpublished data). In contrast, patients with erythema migrans that were treated with antibiotics early in the course of infection appear susceptible to reinfection with *B burgdorferi* since they can develop erythema migrans after new tick bites. This suggests that patients with **chronic** Lyme disease may be immune to reinfection with borreliae while patients with early Lyme disease are not, The fact that some patients with chronic disease do not develop OspA or OspB antibodies further suggests that other *B. burgdorferi* antigens may play a role in protective immunity,”

Radolf Role of outer membrane architecture in immune evasion by *Treponema pallidum* and *Borrelia burgdorferi* Trends Microbiol 1994:
https://www.ncbi.nlm.nih.gov/pubmed/7812663

Determining the precise location of spirochetes within tissues **chronically** infected with *B burgdorferi* has been difficult. However, when spirochetes are visualized in such tissue specimens, they appear to be extracellular. Dissemination of *B burgdorferi* in the blood also occurs in **chronically** infected immunocompetent mice, despite the presence of *B burgdorferi*-specific antibodies. Such observations provide the rationale for studying the molecular architecture of the Lyme-disease spirochete within the context of immune evasion.

In contrast to *T pallidum*, which appears to have no surface lipoproteins, there is overwhelming evidence that borrelial lipoproteins are found on the surface of organisms cultivated in vitro. If these molecules are such accessible immune targets, why are spirochetes not cleared rapidly during natural or experimental infection? This question is even more paradoxical in that sera from **chronically** infected individuals may be borreliacidal in vitro (49). The answer appears to involve both genetic mechanisms for downregulating the expression of surface lipoproteins at various times during infection and also the slective repression of antibody responses against specific proteins, particularly OspA and OspB (Refs 14,40,50). The ultimate effects of these poorly understood dynamic processes are dramatic reductions in both the immunogenicity of the spirochetal surface and the absolute number of targets for potentially borreliacidal antibodies.

Steere Lyme disease: A growing threat to urban populations Proc Natl Acad Sci 1994:
https://www.ncbi.nlm.nih.gov/pubmed/8146126

...Late or persistent infection (stage 3) usually begins months to years later and typically consists of intermittent or **chronic** arthritis (19), **chronic** neurologic involvement (48-51), or acrodermatitis **chronica** atrophicans (52).

Bergstrom Barbour Magnarelli, "Background of the invention" section in U.S. patent description for "DNA encoding *Borrelia burgdorferi* OspA and a method for diagnosing *Borrelia burgdorferi* infection" 12.10.96 (filed 10.3.94):

"In many patients the infection of some tissues, particularly the brain and joints, **persists** for years and can be severely disabling. These forms of **chronic** Lyme disease are a consequence of the host's inability to rid itself of the infectious agent and perhaps the development of an autoimmune reaction (7)

7 = Steere et al, Early clinical manifestations of Lyme disease Ann Intern Med 1983, 99:76-72

Radolf Goldberg Bourell Baker Jones Norgard Characterization of outer membranes isolated from *Borrelia burgdorferi*, the Lyme disease spirochete Infect Immun 1995:
https://www.ncbi.nlm.nih.gov/pubmed/7768594

Humoral immune response against OM proteins during **chronic** Lyme disease. A poorly understood aspect of Lyme disease concerns the inability of host immune responses to eradicate persistent

spirochetal infection. Although rising antibody titers to *Bb* and expanding reactivity to spirochetal antigens have been well documented during persistent infection in a variety of mammalian hosts (39), it is not known how much of this antibody response is directed against surface-exposed borrelial proteins (and, therefore, is capable of contributing to bacterial clearance).

Cox Akins Bourell Lahdenne Norgard Radolf Limited surface exposure of *Borrelia burgdorferi* outer surface lipoproteins Proc Natl Acad Sci USA 1996:
https://www.ncbi.nlm.nih.gov/pubmed/8755587

...Our finding that these highly abundant immunogens have only limited surface exposure prompts a major revision of current concepts of *B burgdorferi* ultrastructure and its relationship to immune evasion during **chronic** Lyme disease.

Norgard Arndt Akins Curetty Harrich Radolf Activation of human monocytic cells by *Treponema pallidum* and *Borrelia burgdorferi* and synthetic lipopeptides proceeds via pathway distinct from that of lipopolysaccharide but involves transcriptional activator NF-kB Infect Immun 1996:
https://www.ncbi.nlm.nih.gov/pubmed/8751937

Syphillis and Lyme disease are **chronic** infections caused by the pathogenic spirochetes *Treponema pallidum* and *Borrelia burgdorferi*, respectively.

The observation that proinflammatory activity is a “generic” property of spirochetal lipoproteins raises the intriguing possibility that lipoproteins unrelated to OspA or OspB which are expressed exclusively during the course of infection can promote the inflammatory processes that engender clinical manifestations in **chronic** Lyme disease. This contention can be evaluated by examining the proinflammatory properties of borrelial lipoproteins expressed exclusively during the mammalian phase of the spirochete life cycle.

Wooten Modur McIntyre Weis *Borrelia burgdorferi* outer membrane protein A induces nuclear translocation of nuclear factor-kappa B and inflammatory activation in human endothelial cells J Immunol 1996:
https://www.ncbi.nlm.nih.gov/pubmed/8906837

...OspA expression can reappear late in disease, and this re-expression may contribute to the inflammation associated with **chronic** Lyme disease (58).

Nanagara, Duray Schumacher Ultrastructural demonstration of spirochetal antigens in synovial fluid and synovial membrane in chronic Lyme disease: Possible factors contributing to persistence of organisms Human Pathology 1996:
https://www.ncbi.nlm.nih.gov/pubmed/8892586

Electron microscopy adds further evidence for **persistence** of spirochetal antigens in the joint in **chronic** Lyme disease. Locations of spirochetes or spirochetal antigens both intracellulary and extracellulary in deep synovial connective tissue as reported here suggest sites at which spirochaetes may elude host immune response and antibiotic treatment.

In our EM study, there was strong evidence of ongoing vascular injury in acute and also in **chronic** Lyme synovium. These feature of vasulopathy were not related to the total duration of arthritis. The signs of active vascular injury, found even in long-standing **chronic** Lyme arthritis (patient 3) may be evidence of repeated microvascular insults, occurring during each episode of arthritis.

If spirochetes are already sequestered in tissue that is inaccessible to antibiotics such as in the fibrinous and collagen tissue or within fibroblasts, high-dose parenteral antibiotics (54), or combination therapies (55, 56) with long duration may be needed to kill the living spirochetes. Failure of antibiotic treatment in **chronic** Lyme arthritis may also be explained by spirochetal antigens that exist in the joint and perpetuate immune response in genetically predisposed patients.

Bunikis Noppa Östberg Barbour Bergström Surface exposure and species specificity of immunoreactive domain of a 66-kilodalton outer membrane protein (P66) of the *Borrelia* spp. that cause Lyme disease Infect Immun 1996:

https://www.ncbi.nlm.nih.gov/pubmed/8945554

...Later, hematogenous spread of the borreliae may occur causing **chronic** dermatologic, neurologic, and arthritic complications...

... These proteins may also contribute to the development of **chronic** Lyme disease by undergoing subtle antigenic changes which give rise to immunoevasive mutants (13,19,20,33).

Norris, Barbour et al, U.S. patent description for "VMP-like sequences of pathogenic Borrelia", 4.13.04 (filed 2.20.97 -> 8.16.02)
Norris, U.S patent description for "VMP-like sequences of pathogenic Borrelia species and strains" 8.25.15 (filed 4.21.14)

"The infection, if untreated, commonly persists for months to years despite the occurrence of host antibody and cellular responses; this observation indicates effective evasion of the immune response. Lyme disease may be disabling (particularly in its **chronic** form), and thus there is a need for effective therapeutics and prophylactic treatment."

Philipp Duray Piesman Xu The outer surface protein A (OspA) vaccine against Lyme disease Efficacy in rhesus monkey Vaccine 1997:

https://www.ncbi.nlm.nih.gov/pubmed/9413097

... although timely administration of appropriate antibiotics is usually curative, long courses of therapy may be required if the infection is allowed to become **chronic**, and in some patients there is no response to therapy at all.

Zhang Barbour Norris Antigenic variation in Lyme by promiscuous recombination VMP-like sequence cassettes Cell 1997:
https://www.ncbi.nlm.nih.gov/pubmed/9108482

... it is likely that VlsE plays an important role in some aspect of infection... and that antigenic variation merely permits surface expression of this protein without leading to elimination of the bacteria by the host's immune response.

Koomey Bacterial pathogenesis: A variation on variation in Lyme Curr Bio 1997:
https://www.ncbi.nlm.nih.gov/pubmed/9285701

Abstract:
The discovery of antigenic variation in *Borrelia burgdorferi*, the bacterium that causes Lyme disease, provides a potential explanation for the **chronic** nature of infection as well as new insights into the genetic structure of highly recombinogenic loci responsible for combinatorial genetic diversification.

... And now the Lyme disease pathogen, *Borrelia burgdorferi* can be added to this list; the recent discovery of antigenic variation in this species may explain the **chronic** nature of Lyme disease.

Barbour Zückert Genome sequencing. New tricks of tick-borne pathogen Nature 1997:
https://www.ncbi.nlm.nih.gov/pubmed/9403678

"Determination of the *B burgdorferi* genome has opened doors for investigation and closed just as many. By understanding the biosynthetic and transport limitations of *B burgdorferi*, we may be able to develop a medium in which to grow as-yet uncultivable *Borrelia* spp. The results encourage study of a more metabolically competent spirochaete, such as the free-living *Spirochaeta aurantia*, for a better understanding of how this ancient group of bacteria evolved, and to identify catalytic molecules of industrial importance. But the sequence does not explain the **persistence** of the disease in some people yet not in others;..."

Phillips Mattman Hulinska Moayad, Proposal for reliable culture of *B burgdorferi* from patients with chronic Lyme, even those previously extensively treated Infection 1998:
https://www.ncbi.nlm.nih.gov/pubmed/9861561

Chronic Lyme disease is a controversial topic. Even after extended antibiotic treatment, **persistent** infection in **chronic** Lyme disease has been strongly suggested by the persistence of borrelial antigen, as demonstrated by polymerase chain reaction (3,4)...

...This study proves that chronic Lyme disease is of **chronic** infectious etiology, and that even antibiotic treatment well in excess of current recommendations is not necessarily curative.

Liang Philipp An immunodominant conserved region within the variable domain of VlsE, the variable surface antigen of *B burgdorferi* J Immunol 1999:
https://www.ncbi.nlm.nih.gov/pubmed/10553085

Discussion

The sequence conservation of the six invariable regions across strain and genospecies barriers indicates that these regions are important in whichever role VlsE may play in the physiology of *B burgdorferi.* One would therefore expect that such sequences are **not** antigenic in hosts with a **chronic** *B burgdorferi* infection or would be otherwise inaccessible to Ab, either because they are conformationally buried withing the VlsE molecule or are unavailable on the spirochetal surface.

[BUT...] In addition, 35 of 41 human serum samples collected in the Northeast and Midwest of the US from patients with acute or **chronic** Lyme disease also reacted with the C6 peptide...

... The immunodominance of IR6 was further underscored by the long term persistence of anti-C6 Abs in infected monkeys and in patients with **chronic** Lyme disease (not shown).

... What then is the role of the antigenicity and immunodominance of IR6? It has been hypothesized that **chronic** host exposure to immunodominant Ags or epitopes diverts the immune system from responding to less antigenic but functionally important Ags or epitopes, thus serving as a protective strategy for **persistent** pathogens (30).

Hemmer Gran Zhao Marques Pascal Tzou Kondo Cortese Bielekova Straus McFarland Houghten Simon Pinilla Martin Identification of candidate T-cell epitopes and molecular mimics in chronic Lyme disease Nature Med 1999:
https://www.ncbi.nlm.nih.gov/pubmed/10581079

In **chronic** infectious diseases such as Lyme disease, immune-mediated damage may add to the effects of direct infection by means of molecular mimicry to tissue autoantigens. Here, we describe a new method to effectively identify both microbial epitopes and candidate autoantigens. The approach combines data acquisition by positional scanning peptide combinatorial libraries and biometric data analysis by generation of scoring matrices. In a patient with **chronic** neuroborreliosis, we show that this strategy leads to the identification of potentially relevant T-cell targets derived from both *Borrelia burgdorferi* and the
host.

In **chronic** CNS lesions, vasculitis and lymphocytic infiltrates both indicate involvement of cell-mediated autoimmunity, but little is known about the specific *B. burgdorferi* antigens that may be involved in CNS Lyme disease. Moreover, information is scarce on which CNS antigens may be relevant as target autoantigens in this condition [5,23].

Coburn (NEMC) **Chege Magoun Bodary** (Genentech) **Leong** (U Mass Worcester) **Characterization of a candidate *Borrelia burgdorferi* ℬ3-chain integrin ligand identified using a phage display library Mol Microbiol 1999:**
https://www.ncbi.nlm.nih.gov/pubmed/10594819

...A remarkable aspect of this infection is that, in the absence of appropriate antibiotic therapy, the bacteria are able to establish **chronic** infection even in the face of an intact immune system...

As is the case in humans, in animals the spirochaete is able to disseminate widely and avoid clearance by the immune system, thereby establishing **chronic** infection.

Straubinger Straubinger Summers Jacobson Status of *Borrelia burgdorferi* infection after antibiotic treatment and the effects of corticosteroids: An experimental study J Infect Dis 2000:
https://www.ncbi.nlm.nih.gov/pubmed/10720533

… Patients with acute Lyme borreliosis are normally highly responsive to therapy and even chronic cases shows a favorable response to antibiotic treatment (23). However, patients may show relapses weeks to years after antibiotic therapy (24), which raises the question of reinfection or reactivation of the primary infection. It appears that *B burgdorferi* can survive antibiotic therapy either by residing in privileged sites provided by the host or by using other strategies…

In conclusion, the canine model of acute Lyme arthritis has provided further insight into this disease. We were able to investigate the status of the infection >360 days after antibiotic treatment and to collect data relevant to the chronic course of the disease seen in humans. We demonstrated that **chronic** silent infection with *B burgdorferi* can be converted into active disease. Positive PCR results after therapy may reflect low-level persistent infection. Further research is needed to uncover the mechanisms that enable *B burgdorferi* to gain a permanent foothold in the mammalian host.

Straubinger (College of Veterinary Medicine, Cornell) **PCR-based quantification of *Borrelia burgdorferi* organisms in canine tissues over 500-day postinfection period J Clin Micro 2000:**
https://www.ncbi.nlm.nih.gov/pubmed/10834975

In this study, q-PCR was used to quantify *B burgdorferi* populations in skin tissue and blood samples of beagle dogs collected sequentially over a period of more than 500 days. To determine whether the number of borrelia organisms is correlated with clinical disease and whether antibiotic therapy eliminates the organisms in tissues, three groups of four dogs were each treated with different antibiotics for a 30-day period, and data for these animals were compared to those for untreated dogs. This experimental model was used because Lyme borreliosis is very similar to the disease in humans (1,28). Our studies have shown that despite a vigorous immune response of the dog, *B burgdorferi* is not eliminated and the bacterium establishes a **persistent** infection, particularly in collagen-rich tissue (10).

In summary, real-time PCR allowed a quantitative insight into the host-bacterium interaction in canine Lyme borreliosis: … (iii) antibiotic therapy reduced the load of *B burgdorferi* organisms in the host but failed to eradicate the agent. This technique will benefit future studies designed to solve the exact mechanisms by which *B burgdorferi* establishes a **persistent** infection and triggers an inflammatory response in tissue.

Beerman Lochnit Geyer Groscurth Filgueira The lipid component of lipoproteins from *B burgdorferi* Structural analysis, antigenicity and presentation via human dendritic cells Biochem Biophys Comm 2000:
https://www.ncbi.nlm.nih.gov/pubmed/10673388

Borrelia burgdorferi sensu stricto strain LW2 [27], a tendon isolate of a patient suffering from **chronic** Lyme disease...

Lyme borreliosis is characterized by **chronic** manifestations that coexist with a measurable immune response

Seshu Skare The many faces of *Borrelia burgdorferi* J Mol Microbiol Biotech 2000:
https://www.ncbi.nlm.nih.gov/pubmed/11075919

Identification of such variable determinants may shed light on additional escape variants selected for by the host and would help explain the **chronic** infection associated with Lyme borreliosis.

Pachner Cadavid Shu Dail Pachner Hodzic Barthold Central and peripheral nervous system infection, immunity and inflammation in the NHP model of Lyme borreliosis Ann Neurol 2001:
https://www.ncbi.nlm.nih.gov/pubmed/11558789

Abstract: … These data demonstrate that Lyme neuroborreliosis is a **persistent** infection, that spirochetal presence is a necessary but not sufficient condition for inflammation, and that antibody measured in serum may not predict the severity of infection.

This manuscript presents for the first time a combined analysis of spirochetal load, immunological response to the spirochete in the CSF and serum, and inflammation in infected tissues in a large group of animals in the NHP [nonhuman primate] model of LNB [Lyme neuroborreliosis]. The work showed that *B burgdorferi* is widely disseminated throughout the central and peripheral nervous system, a strong host immune response attacks the spirochete but is unable to clear the organism, and there is widespread inflammation in which presence of spirochete is necessary but not sufficient to cause inflammation.

Burgdorfer, Arthropod Borne Spirochetoses: Historical Perspective Eur J Clin Microbiol Infect Dis 2001:
https://www.ncbi.nlm.nih.gov/pubmed/11245316

This test is presently hailed as a potential breakthrough for reliable diagnosis of Lyme disease in patients with late or **chronic** illness.

Martin (NINDS/NIH) **Gran Zhao Markovic-Plese Bielekova Marques** (NIAID/NIH) **Sung Hemmer** (NINDS/NIH, Univ Marburg) **Simon McFarland Pinilla** (Torrey Pines

Institute, San Diego) **Molecular mimicry and antigen-specific T cell responses in MS and chronic CNS Lyme disease J Autoimmunity 2001:**

https://www.ncbi.nlm.nih.gov/pubmed/11334482

We already utilized this search strategy for the identification of both *B burgdorferi*-derived sequences, the causative agent of Lyme disease, and to human proteins, for a clone (CSF-3) that was isolated from the CSF of a patient with **chronic** CNS Lyme disease (25 = Hemmer et al *Nature Med* 1999).

Hudson (USDA, Athens, GA) Frye Quinn **Gherardini** (Univ Georgia, Athens) **Increased expression of *B burgdorferi* vlsE in response to human endothelial cell membranes Mol Microbiol 2001:**
https://www.ncbi.nlm.nih.gov/pubmed/11454215

As *B burgdorferi* disseminates to various sites in the body, other cell types and conditions are encountered, which could trigger additional changes in gene expression that are essential for maintaining an infection. Identifying the genes that are involved in establishing and maintaining a **chronic** infection is essential for understanding the pathogenesis of Lyme disease.

McDowell Sung Hu Marconi Evidence that variable regions of central domain of VlsE are antigenic during infection with Lyme disease spirochetes Infect Immun 2002:
https://www.ncbi.nlm.nih.gov/pubmed/12117928

The **chronic** nature of Lyme disease and the genetic and antigenic diversity of the Lyme disease spirochetes suggest that antigenic variation may play an important role in immune evasion.

Vrethem Hellblom Widlund Ahi Danielsson Emerudh Forsberg Chronic symptoms are common in patients with neuroborreliosis — a questionnaire follow-up study Acta Neurol Scand 2002:
https://www.ncbi.nlm.nih.gov/pubmed/12225315

OBJECTIVES:
The existence of chronic neuroborreliosis is controversial. The aim of our study was to investigate the existence and kind of *persistent symptoms in patients previously treated* because of neurological symptoms as a result of neuroborreliosis.

MATERIALS AND METHODS:
A total of 106 patients with neuroborreliosis, according to established criteria, and a control group of 123 patients with Borrelia induced erythema migrans diagnosed in a general practitioner office were studied. A questionnaire was sent to patients and controls concerning their health situation. Time from onset of neurological symptoms to the questionnaire send out was 32 months (mean) for the patients with neuroborreliosis and 33 months (mean) for the controls.

RESULTS:

Fifty per cent of the individuals in the patient group compared with 16% of the individuals in the control group showed **persistent** complaints after their Borrelia infection ($P < 0.0001$). The most significant differences between the groups were the presence of neuropsychiatric symptoms such as headache, attention problems, memory difficulties and depression. Paresthesia, pain and persistent facial palsy was also significantly more common in patients treated because of neuroborreliosis.

CONCLUSION:
Our study shows that **persisting** neurological symptoms are common after a neuroborreliosis infection. The pathological mechanisms that lay behind the development of **chronic** symptoms, however, are still uncertain.

Widhe Ernerudh (Univ Linkoping, Sweden) **Cytokines in Lyme borreliosis Lack of early TNF-alpha and transforming growth factor-beta responses are associated with chronic neuroborreliosis Immunology 2002:**
https://www.ncbi.nlm.nih.gov/pubmed/12225362

In Europe, neuroborreliosis (NB) is a common manifestation, with the risk of developing into a chronic disease. Several reports suggest the occurrence of **persistent** or **reappearing** neurological symptoms in 20-50% of NB patients treated (3-5).

Diterich Hartung *B burgdorferi* induced tolerance as model of persistence via immunosupression Infection Immunity 2003:
https://www.ncbi.nlm.nih.gov/pubmed/12819085

"If left untreated, infection with *B burgdorferi* sensu lato may lead to **chronic** Lyme borreliosis. It is still unknown how this pathogen manages to persist in the host in the presence of competent immune cells." [p.3979]

"If infection with this pathogen is not treated adequately with antibiotics, it may lead to a **chronic** multisystemic disorder which is difficult to cure." [p.3979]

"Blood cells from patients sufffering from **persistent** LB released significantly lower levels of proinflammatory cytokines (i.e. TNF-alpha and gamma interferon) in response to either a Borrelia-specific stimulus or LPS than cells from healthy volunteers (8). [p. 3979]

"Understanding the immunopathology of LB is still a major challenge. Although it induces strong immune activation, e.g. in phases of arthritis, the causative agent of LB persist and leads to a **chronic** pathology in the immunocompetent host. Of note, the inflammatory episodes associated with LB are typically self-limiting and the site of manifestation often changes, e.g. between different joints. These phenomena suggest counterregulatory anti-inflammatory mechanisms, and the long phases of latency indicate phases of immune evasion. [p. 3984-85]

Ekerfelt Jarefors Tynngard Hedlund Sander Bergstrom Forsberg Ernerudh Phenotypes indicating cytolytic properties of Borrelia-specific interferon-gamma secreting cells in chronic Lyme neuroborreliosis J Neuroimmunol 2003:
https://www.ncbi.nlm.nih.gov/pubmed/14644037

Abstract:
The immuno-pathogenetic mechanisms underlying **chronic** Lyme neuroborreliosis are mainly unknown. Human Borrelia burgdorferi (Bb) infection is associated with Bb-specific secretion of interferon-gamma (IFN-gamma), which may be important for the elimination of Bb, but this may also cause tissue injury. In order to increase the understanding of the pathogenic mechanisms in **chronic** neuroborreliosis, we investigated which cell types that secrete IFN-gamma. Blood mononuclear cells from 13 patients with neuroborreliosis and/or acrodermatitis chronicum atrophicans were stimulated with Bb antigen and the phenotypes of the induced IFN-gamma-secreting cells were analyzed with three different approaches. Cells expressing CD8 or TCR gamma delta, which both have cytolytic properties, were the main phenotypes of IFN-gamma-secreting cells, indicating that tissue injury in **chronic** neuroborreliosis may be mediated by cytotoxic cells.

Singh Girschick Toll-like receptors in *B burgdorferi*-induced inflammation Clin Microbiol Infect 2006:

https://www.ncbi.nlm.nih.gov/pubmed/16842565

Although *B. burgdorferi* can induce a strong bactericidal immune activation, e.g., in phases of arthritis, the causative agent of Lyme borreliosis seems to be able to **persist** in humans, which probably contributes to a **chronic** pathology in the immunocompetent host (11). A **remitting and episodic** course of inflammation has been described, indicating a repetitive confrontation of the immune system with spirochaetal components (43).

Cassiani-Ingoni Cabral Marques Martin *B burgdorferi* induces TLR1 and TLR2 in human microglia and peripheral blood monocytes but differentially regulates HLA-class II expression J Neuropathol Exp Neurol 2006:

https://www.ncbi.nlm.nih.gov/pubmed/16783164

Because nervous system manifestations of Lyme disease occur frequently, besides the **chronic** involvement of the skin, the heart, and the joints, and because the CNS is considered an immunoprivileged organ, it is important to understand which factors contribute to tissue inflammation in the CNS.

Larsson Andersson Pelkonen Guo Nordstrand Bergstrom Persistent brain infection and disease reactivation in relapsing fever borreliosis Microbes Infect 2006:

https://www.ncbi.nlm.nih.gov/pubmed/16782384

The closely related spirochetal pathogens *Borrelia burgdorferi sensu lato* and *Treponema pallidum* are associated with **persistent** disease and infection of the brain, causing neurological disorders denoted Lyme neuroborreliosis and neurosyphilis, respectively...

...We hypothesized that like Lyme disease and syphilis, certain relapsing fever infections may be **persistent** in nature, providing a bacterial reservoir for potential infection of naive vectors...

...Intriguingly, *B duttonii* is far more persistent in the blood than the other species tested, and can cause a quantifiable persistent residual brain infection for at least 270 days. In addition, host immunosuppression enables these bacteria to re-enter the blood and achieve densities similar to those of the initial infection. We also present further evidence of bacterial immune evasion since animals with residual brain infection display a gene expression profile consistent with uninfected controls. Thus, the experiments in this study challenge the current paradigm of relapsing fever as an acute disease to include in some cases silent infection, in which bacteria can **persist** in an immune privileged site that provides a reservoir for reactivation.

Cabello Godfrey Newman Hidden in plain sight: *B burgdorferi* and extracellular matrix Trends in Microbiol 2007:
https://www.ncbi.nlm.nih.gov/pubmed/17600717

Better knowledge of ... genetic and structural bases for these interactions of *Bb* with extracellular matrix will be required before understanding of **persistence** of *Bb* in tissues and development of **chronic** infections can be achieved

Bb... causes a **chronic** extracellular infection [2]}

Here we suggest that these interactions are of great importance in **chronic** infections with this organism

Interaction of *B burgdorferi* with ECM is important for chronic infection

Interaction between Bb with the ECM (24), a hydrated complex of fibrous and non-fibrous proteins and proteoglycans, and specifically collagen (or its associated molecules), appears to be essential for persistence and **chronic** infection.

…ability of this pathogen to produce acute and **chronic** infections.

Grygorczuk et al (Poland) **Concentration of TGF-beta1 in supernatant of PBMCs cultures from patients with early disseminated and chronic Lyme borreliosis Adv Med Sci 2007:**
https://www.ncbi.nlm.nih.gov/pubmed/18217413

Hodzic Barthold Persistence B burgdorferi following antibiotic treatment in mice Antimicrob Agents Chemother 2008:
https://www.ncbi.nlm.nih.gov/pubmed/18316520

Abstract: … Results indicated that following antibiotic treatment, mice remained infected with nondividing but infectious spirochetes, particularly when antibiotic treatment was commenced during the **chronic** stage of infection.

The current study further investigated the issue of B burgdorferi persistence following antibiotic therapy by examining mice treated with ceftriaxone during the early stage of infection compared to mice treated during the late stage of infection. A recent study has shown that there are significant shifts into or

preferential survival of spirochetes in collagen during **chronic** infection (7), which may facilitate immune evasion and impact effectiveness of antibiotics.

Xu Liang (LSU) **Modification of *B burgdorferi* to overproduce OspA or VlsE alters its infectious behavior Microbiology 2008:**
https://www.ncbi.nlm.nih.gov/pubmed/18957595

Within mammals, however, *ospA* expression is essentially repressed, while *vlsE* expression is unregulated, especially during **chronic** infection of immunocompetent hosts (Liang et al, 2004b).

After dissemination, humoral responses greatly upregulate vlsE in all tissues, an event consistent with the critical role of VlsE in immune evasion during **chronic** infection of immunocompetent hosts (Bankhead & Chaconas, 2007; Zhang et al, 1997).

Barthold Hodzic Imai Feng Yang Luft Ineffectiveness of tigecycline against persistent *B burgdorferi* Antimicrob Agents Chemother 2010:
https://www.ncbi.nlm.nih.gov/pubmed/19995919

... the immune system is needed to fully eliminate the remaining spirochetes. However, therein lies the challenge, since *Borrelia burgdorferi* has evolved to **persistently infect** fully immunocompetent hosts. **Persistent infection** has been shown to be **the rule, rather than the norm, in a variety of laboratory animal species**, including mice, rats, *Peromyscus leucopus*, hamsters, gerbils, guinea pigs, rabbits, dogs, and nonhuman primates. Based upon culture and/or PCR, **persistent infections** have also been documented in humans from both Europe (3,36,43,46,65,67,71,74) and the US (14,19,47). Therefore, the “mop up” phase, which is dependent upon the immune system, is likely to be ineffective against an agent such as *B burgdorferi*, which is highly effective at evading host clearance.

... At all phases of these events, spirochetes cannot be cultured, and their numbers are very low, suggesting a viable but slowly dividing or nondividing population (27). These features fit the paradigm of multidrug tolerance or “recalcitrance to eradication” by antibiotics that occurs among a variety of persistent bacterial and fungal infections (reviewed in references 30,38, 39).

These results challenge prevailing dogma about effectiveness of antibiotics for eliminating *B burgdorferi* infection, and therefore further work is critically needed.

Embers Barthold Borda Bowers Doyle Hodzic Jacobs Hasenkampf Martin Narasimhan Phillippi-Falkenstein Purcell Ratterree Philipp Persistence of *Borrelia burgdorferi* in rhesus macaques following antibiotic treatment of disseminated infection PLoS One 2012:
https://www.ncbi.nlm.nih.gov/pubmed/22253822

…These results demonstrate that *B. burgdorferi* can withstand antibiotic treatment, administered post-dissemination, in a primate host. Though *B. burgdorferi* is not known to possess resistance mechanisms and is susceptible to the standard antibiotics (doxycycline, ceftriaxone) in vitro, it appears to become tolerant post-dissemination in the primate host. This finding raises important questions about the

pathogenicity of antibiotic-tolerant persisters and whether or not they can contribute to symptoms post-treatment.

Muller Damage collagen elastic fibres by *B burgdorferi* - Known and new clinical histopathological aspects Open Neuro 2012:

https://www.ncbi.nlm.nih.gov/pubmed/23986790

"Tendons and ligaments are a structurally and topographically ideal retreat for Borrelia. Their involvement is a further factor to indicate a **chronic** course of the disease. Serological antibody diagnostic techniques proved to be inadequate in cases such as this, possibly because the formation of antibodies is inhibited by the pathogen [11]""

Kenedy Lenhart Akins The role of *B burgdorferi* outer surface proteins FEMS Immunology and Med Microbiol 2012:

https://www.ncbi.nlm.nih.gov/pubmed/22540535

These spirochetes are unique in that they can cause **chronic** infection and persist in the infected human, even though a robust humoral and cellular immune response is produced by the infected host.

Infected individuals that do not receive antibiotic therapy are at risk for developing **chronic** forms of the disease which can result in various disorders of the heart, nervous system, and joints.

13th International Conference on Lyme borreliosis and other tick borne diseases - Boston - Aug 2013:

https://www.frontiersin.org/books/13th_International_Conference_on_Lyme_Borreliosis_and_other_tick_Borne_Diseases_/357

Abstract A066 (D054) - p.114
Nepereny Vrzal (Bioveta, Czech Republic) **Sensitivity of different *Borrelia* genospecies to dog serum complement**

Lyme disease is a **chronic** multisystem infectious disease that is the most common arthropod-borne infectious disease both in Europe and in the United States.

Abstract A083 (P045) - p. 128
Troy Norris Hu (Tufts, U Texas Houston) **Understanding barriers to *B burgdorferi* dissemination during infection using massively parallel sequencing**

B burgdorferi is an invasive spirochetal pathogen that can cause acute and **chronic** infections in the skin, heart, joints and central nervous system of infected mammalian hosts. Following transmission into a mammalian host through the bite of an *Ixodes scapularis* tick, the bacteria establish infection at the inoculation site and then quickly disseminate to distal tissues initiating **long-term colonization**. In this process, *B burdorferi* encounters multiple potential barriers to infection including adapting to

environmental changes in nutrients, pH and temperature, breaking through tissue barriers to invasion and dissemination, and evading host immune responses.

Abstract B017 (P016) - p.150
Embers Jacobs (Tulane Primate Research Ctr, Covington, LA) **Tick-mediated *B burgdorferi* infection on nonhuman primates for assessment of antibiotic efficacy**

... The causative agent, *B burgdorferi*, can **chronically** infect humans, causing rash, arthritis, carditis, and neurological dysfunction.

Abstract B029 (D021) - p. 162
Blenk (EuromedClinic, Fuerth, Germany) **Straubinger Schuster Ünsal-Kirici Steinhaven Schütt Komorowki** (EUROIMMUN AG, Luebeck, Germany) **Relevance of quantitative determination of IgG antibodies against VlsE as an activity marker in the monitoring of treated Lyme borreliosis: A retrospective study**

Archived (-80C) sera from patients with confirmed or suspected Lyme disease from our Lyme outpatient clinic were used as sample material.

Results: A significant drop in the titer of anti-VlsE antibodies could be detected as early as 6-8 weeks after successful treatment in all active **chronic** Lyme infections, inc Lyme arthritis, ACA, acute neuroborreliosis and other active **chronic** stages of Lyme infection. This decrease in anti-VlsE correlated with a reduction in clinical symptoms. The absence of an anti-VlsE titer virtually excludes a florid **chronic** Lyme infection (control panel of healthy individuals, n=105). Strongly positive anti-vlsE values (>1000 RU/ml) in untreated patients are to 99% an indication of an active **chronic** Lyme infection.

Conclusion: Quantitative determination of anti-VlsE IgG is suitable - always under consideration of clinical symptoms - for confirmation of diagnosis and as an activity marker for monitoring patients with active **chronic** Lyme borreliosis before and after treatment.

Abstract B037 (D035) - p.170
Chan Marras Schutzer Parveen Development of a novel nucleic acid-based diagnostic assay for Lyme disease:

The infection with *Borrelia burgdorferi* can result in acute to **chronic** Lyme disease... We anticipate that pre-enrichment of the spirochetes present in the blood by culture before conducting the rt-PCR will further improve sensitivity and specificity of the assay such that it can be used as a diagnosis of early to **chronic** stages of infection by Lyme spirochetes

Abstract B048 (D055)
Eshoo Crowder Schutzer Aucott Direct molecular detection of *B burgdorferi* from whole blood and CSF of patients with acute and chronic Lyme disease (revised)

… Results will also be presented on the analysis of a large set (>200) of CSF specimens collected in Germany from patients with acute and **chronic** neuroborreliosis.

Abstract B053
Reye Muller (Nat'l Public Health Lab, Luxembourg) **From prevalence studies to the development of novel diagnostic tests for Lyme disease**

Therefore, antigen-specific B-cells will be isolated and compared on a single cell level between acute, **chronic**, and resolved patients.

Abstract B076 (D018) - p. 207
Guadulupe Javier Lyme neuroborreliosis is highly prevalent in tertiary care hospitals of Central-southeast Mexico

Results: We studied 650 patients and confirmed Lyme Neuroborreliosis in 132 (20.3%). The acute disseminated stage was documented ion 100 (75.7%) with facial palsy, lymphocytic meningitis, poliradiculopathy 27 cases, and the **chronic** stage in 32 (24%) of the cases with encephalomyelitis.

Conclusions: This is the first report of Lyme neuroborreliosis in central of Latin-American, and presents as disseminated and a **chronic** stage.

Kelesidis Cross talk between spirochetal lipoproteins and immunity Frontiers Immunol 2014:

https://www.ncbi.nlm.nih.gov/pubmed/25071771

"Lipopeptides in combination with other antigens from spirochetes facilitates the transition from innate to prolonged adaptive immune responses that contribute to **chronic** manifestations of spirochetal diseases such as syphilis and Lyme disease (11). "

Hodzic Imai Feng Barthold Resurgence of persisting non-cultivable *Borrelia burgdorferi* following antibiotic treatment in mice PLoS One 2014:

https://www.ncbi.nlm.nih.gov/pubmed/24466286

Abstract: The agent of Lyme borreliosis, *Borrelia burgdorferi*, evades host immunity and establishes persistent infections in its varied mammalian hosts. This persistent biology may pose challenges to effective antibiotic treatment. Experimental studies in dogs, mice, and non-human primates have found persistence of *B. burgdorferi* DNA following treatment with a variety of antibiotics, but persisting spirochetes are non-cultivable. Persistence of B. burgdorferi DNA has been documented in humans following treatment, but the significance remains unknown…

Experimental animal studies have shown that *Borrelia burgdorferi*, the agent of Lyme borreliosis, consistently establishes persistent infections in a variety of immunocompetent hosts, including laboratory mice (1), white-footed mice (*Peromyscus leucopus*) (2,3,4), rats (5), hamsters (6), guinea pigs (7), gerbils (8), dogs (9), and nonhuman primates, including rhesus macaques (*Macaca mulatta*) (10) and baboons (*Papio spp.*) (11). Clinical evidence extends this paradigm to humans (12). Persistence is an essential strategy for a complex *B burgdorferi* life cycle in both ticks and reservoir hosts, and likely pertains to

incidental hosts, such as humans. Persistent biology may pose a challenge in antibiotic therapy, though antibiotics ameliorate the majority of host persisting bacteria, by virtue of their immune-evasion biology, may survive in hosts that are unable to clear infection.

Discussion
This study validates a mouse model that can be used for investigation of post-antibiotic persistence of non-cultivable *B burgdorferi*…

Results of this study demonstrated not only **persistence**, but also **resurgence** of non-cultivable *B burgdorferi* in tissues of mice at up to 12 months following antibiotic treatment, despite the continued inability to culture spirochetes fro the tissues…

Although various animal studies may each have their flaws (as do human clinical studies), the comparative evidence in dogs, mice, non-human primates, and perhaps humans, is compelling, and suggests that something unique is happening with *B burgdorferi* following antibiotic treatment…

Rogovskyy (College Vet Med,Texas A&M) **Zelikovsky** (Dept Computer Sci, Georgia State Univ) **Antibody response to Lyme disease spirochetes in context of VlsE-mediated immune evasion Infect Immun 2016:**
https://www.ncbi.nlm.nih.gov/pubmed/27799330

When missed and therefore left untreated, LD becomes **chronic**, presenting itself as skin lesions, arthritis, and carditis and occasionally with subsequent nervous system involvement.

Grillon Westermann Cantero Jaulhac Voordouw Kapps Collin Barthel Ehret-Sabatier Boulanger identification of *Borrelia* protein candidates in mouse skin for potential diagnosis of disseminated Lyme borreliosis Nature Sci Rep 2017:
https://www.ncbi.nlm.nih.gov/pubmed/29196626

In competent reservoir hosts, *Borrelia* pathogens establish a c**hronic** infection in the skin and other organs such as the heart, bladder and joints.

15th International Conference on Lyme borreliosis and other tick borne diseases - Atlanta - Sept 2018:

Poster P51
Crowley Casselli (Univ ND) **Highland** (USDA) **Tourand Bankhead** (Wash State Univ) **A novel plasmid-encoded factor is essential for efficient colonization of host tissues by the Lyme disease spirochete:**

With over 300,000 cases per year, Lyme disease is the most common tick-borne disease in North America. While antibiotic therapies exist, they are only effective when administered soon after exposure, which is challenging given the difficulty of diagnosis and detection of the etiological agent, *B burgdorferi*, in infected patients. The most dangerous aspect of infection with *B burgdorferi* is the pathogen's ability to disseminate from the blood stream and colonize distal tissues, leading to **chronic** and potentially severe disease manifestations.