

# Counterpoint: Long-Term Antibiotic Therapy Improves Persistent Symptoms Associated with Lyme Disease

Raphael B. Stricker

International Lyme and Associated Diseases Society, Bethesda, Maryland

(See the point by Auwaerter on pages 143–8)

**Background.** Controversy exists regarding the diagnosis and treatment of Lyme disease. Patients with persistent symptoms after standard (2–4-week) antibiotic therapy for this tickborne illness have been denied further antibiotic treatment as a result of the perception that long-term infection with the Lyme spirochete, *Borrelia burgdorferi*, and associated tickborne pathogens is rare or nonexistent.

**Methods.** I review the pathophysiology of *B. burgdorferi* infection and the peer-reviewed literature on diagnostic Lyme disease testing, standard treatment results, and coinfection with tickborne agents, such as *Babesia*, *Anaplasma*, *Ehrlichia*, and *Bartonella* species. I also examine uncontrolled and controlled trials of prolonged antibiotic therapy in patients with persistent symptoms of Lyme disease.

**Results.** The complex “stealth” pathology of *B. burgdorferi* allows the spirochete to invade diverse tissues, elude the immune response, and establish long-term infection. Commercial testing for Lyme disease is highly specific but relatively insensitive, especially during the later stages of disease. Numerous studies have documented the failure of standard antibiotic therapy in patients with Lyme disease. Previous uncontrolled trials and recent placebo-controlled trials suggest that prolonged antibiotic therapy (duration, >4 weeks) may be beneficial for patients with persistent Lyme disease symptoms. Tickborne coinfections may increase the severity and duration of infection with *B. burgdorferi*.

**Conclusions.** Prolonged antibiotic therapy may be useful and justifiable in patients with persistent symptoms of Lyme disease and coinfection with tickborne agents.

Lyme disease is a controversial illness [1–6]. The classic features of the disease include receipt of a tick bite followed by the so-called erythema migrans or “bullseye” rash and significant joint swelling typical of arthritis. Unfortunately, the classic features of this tickborne disease are not always present. For example, only 50%–60% of patients with Lyme disease recall having received a tick bite, and often the erythema migrans rash is absent or not in the shape of a bullseye [5, 6]. According to health departments around the United States, the typical bullseye rash is only reported in 35%–

60% of patients with Lyme disease [7, 8]. Furthermore, frank arthritis is only seen in 20%–30% of patients with Lyme disease [1, 2]. Thus, the classic features of the disease may be absent, and the diagnosis may be easily missed [1–4].

In the absence of typical features of Lyme disease, patients may go on to develop a syndrome with multiple nonspecific symptoms that affect various organ systems, including the joints, muscles, nerves, brain, and heart. The myriad symptoms prompt the question whether this is “post-Lyme disease syndrome,” a poorly defined entity triggered by Lyme disease, or whether these symptoms are caused by persistent infection with the Lyme spirochete, *Borrelia burgdorferi*. To address this question, we must first examine the pathophysiology of the disease.

## PATHOPHYSIOLOGY OF LYME DISEASE

*B. burgdorferi* is a fascinating bacterium [9, 10]. It has >1500 gene sequences with at least 132 functioning

Received 19 February 2007; accepted 21 February 2007; electronically published 5 June 2007.

This is a modified version of a paper presented at the 44th Annual Meeting of the Infectious Diseases Society of America, Toronto, Canada, October 2006.

Reprints or correspondence: Dr. Raphael B. Stricker, 450 Sutter St., Ste. 1504, San Francisco, CA 94108 (rstricker@usmamed.com).

**Clinical Infectious Diseases** 2007;45:149–57

© 2007 by the Infectious Diseases Society of America. All rights reserved.  
1058-4838/2007/4502-0002\$15.00

DOI: 10.1086/518853

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 [9, 10].

In addition to its complex genetic makeup, *B. burgdorferi* engages in so-called “stealth pathology” to evade the human immune response [11–50]. Stealth pathology involves 4 basic strategies: immunosuppression; genetic, phase, and antigenic variation; physical seclusion; and secreted factors (table 1). These strategies are outlined below.

## 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 [11–13]. *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 [14–19].

## GENETIC, PHASE, AND ANTIGENIC VARIATION

*B. burgdorferi* engages in genetic, phase, and antigenic variation that shares various features with other organisms [20–23]. 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 [24–29]. 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 [30].

Although antibiotic resistance associated with gene mutation was previously thought to be rare in *B. burgdorferi* infection [31], recent studies have demonstrated gene mutations in the Lyme spirochete that confer in vitro resistance to various antibiotics [32, 33]. 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 [34–43]. In culture, *B. burgdorferi* can be grown in fibroblasts for >8 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 [38–42].

## SECRETED FACTORS

There are a number of factors that are secreted either by *B. burgdorferi* itself or in response to infection with the spirochete [44–51]. For a number of years, it has been known that *B. burgdorferi* secretes a hemolysin, although its function is uncertain [44]. 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 [45].

Even more recently, *B. burgdorferi* was found to secrete pheromones, including AI-2, which is also secreted by mycobacteria [46–50]. 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 [46–50]. In addition, *B. burgdorferi* can induce secretion of aggrecanase, an enzyme that damages cartilage [51]. 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.

## LABORATORY TESTING

Let’s turn briefly to laboratory testing in Lyme disease. A major problem is that current commercial Lyme serologic tests are not sensitive enough for diagnosis, especially during the later stages of disease [52–64]. The Centers for Disease Control and Prevention (CDC) advocates a “2-tier” testing system using an ELISA or immunofluorescence assay as a screening test, followed by a Western blot for confirmation if the result of the ELISA or immunofluorescence assay is positive. The CDC cautions, however, that the 2-tier system should only be used for surveillance purposes and not for diagnosis, and the reason for this warning is clear: although the 2-tier system has a very high specificity (99%–100%), thus avoiding the false-positive results that are the bane of surveillance statistics, it has relatively poor

**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 ( <i>Neisseria</i> species)   |
| Dormant state, autoinduction ( <i>Mycobacterium</i> species)  |
| Fibronectin binding ( <i>Staphylococcus</i> and <i>Streptococcus</i> 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)  |

---

**NOTE.** See text for explanation and references.

sensitivity (50%–75%), which limits its use as a diagnostic test for individual patients.

Other problems with current Lyme disease testing include omission of highly specific bands from the commercial Western blot, sex differences in test reactivity, and limitations of molecular testing, and these issues have been discussed in detail elsewhere [1, 56, 60–63]. Thus, the diagnosis of Lyme disease remains problematic, with as many as one-half of patients experiencing failure with the current 2-tier testing approach [52–64].

## TREATMENT OF LYME DISEASE

With this background concerning the clinical diagnostic problems, complex pathophysiology, and testing difficulties related to *B. burgdorferi*, we arrive at the topic of this debate, which is treatment failure in Lyme disease. Documented treatment failure with culture-confirmed *B. burgdorferi* infection was first reported >17 years ago by Preac-Mursic et al. [65], so it was surprising to see a quotation in the *New York Times* by 2 members of the Infectious Diseases Society of America (IDSA) Lyme disease guidelines committee stating that “[there] is no credible scientific evidence for the persistence of symptomatic *B. burg-*

*dorferi* infection after antibiotic treatment” [66]. Let’s review the “credible scientific evidence” for persistence of this infection taken from articles published over the past 17 years.

## ANIMAL MODELS

We can start with animal models of Lyme disease [67–75]. In the mouse, one study found that “persistence of spirochetes within macrophages provides a possible pathogenetic mechanism for chronic or recurring Lyme disease” [67, p. 909]. In another study, “nine months after treatment, low levels of spirochete DNA could be detected by real time PCR in a subset of antibiotic treated mice” [68, p. 1430]. So at least in the mouse model, spirochetes may persist after appropriate treatment.

Next is the dog model—a particularly convincing model, because Straubinger et al. [69] revealed that, in dogs that had been experimentally infected with *B. burgdorferi* by tick exposure, treatment with high doses of amoxicillin or doxycycline for 30 days diminished persistent infection but failed to eliminate it. Furthermore, when dogs were observed for a 500-day postinfection period (the equivalent of 3–4 human years), *B. burgdorferi* DNA was detectable at low levels in multiple tissue samples obtained from the dogs, despite the administration of “adequate” antibiotic treatment [70].

Finally, in a model using our closest relative, the nonhuman primate macaque monkey, Pachner and colleagues [71–75] found that neurologic and cardiac disease were associated with persistent infection in these monkeys, and cytokine and gene expression related to persistent *B. burgdorferi* infection could be demonstrated >3 months after infection. In summary, these animal models provide “credible scientific evidence” for persistent infection in Lyme disease.

## HUMAN STUDIES

Turning to human studies, there are a number of reports that show persistent symptoms of Lyme disease after short-term antibiotic therapy [76–96]. Persistent symptoms have been noted in 25%–80% of patients with Lyme disease after 2–4 weeks of antibiotic therapy [76–87]. Furthermore, infection that was determined to be persistent on the basis of either culture or PCR evidence has been documented in up to 40% of patients following receipt of the “adequate” antibiotic treatment recommended by the IDSA [88–96]. For example, positive culture and PCR results were found in synovium and synovial fluid specimens obtained from a patient 7 years after treatment [92], and a positive result was reported for a culture of an iris biopsy specimen obtained from a treated patient [93]. These reports suggest that short-term antibiotic therapy may suppress the Lyme spirochete but not eradicate it.

In another case, the patient’s condition deteriorated despite receipt of repeated courses of antibiotic treatment over a 2-

**Table 2. Results of placebo-controlled trials of antibiotic treatment in chronic Lyme disease.**

| Study                 | Year | Treatment   | Results  | Comments   |
|-----------------------|------|---|--|--|
| Klempner et al. [101] | 2001 | IV Ctri for 4 weeks followed by oral doxycycline for 2 months vs. placebo | No improvement in fatigue or quality of life   | Study was criticized because subjects had been sick an average of 4.7 years, and similar treatment had already failed; the treatment regimen was inadequate for degree of functional impairment [104]  |
| Krupp et al. [102]    | 2003 | IV Ctri for 4 weeks vs. placebo   | SI in fatigue noted in 64% of treatment group, compared with 19% of control group; no improvement in cognition | The exact duration of illness was not stated (at least 6 months), and the treatment duration was relatively short; previously untreated patients fared significantly better than control subjects in terms of fatigue improvement (69% vs. 0%; $P < .01$ ) |
| Fallon [105]          | 2005 | IV Ctri for 10 weeks vs. placebo  | SI in cognitive and physical functioning at 12 weeks in treatment group, compared with control group           | Improvement in physical functioning but not cognitive functioning was sustained in the treatment group at 24 weeks   |
| Cameron [106]         | 2005 | Oral amoxicillin for 3 months vs. placebo                                 | SI in cognitive and physical functioning in treatment group, compared with control group                       | Treatment was successful in two-thirds of the patients who had the best initial quality of life, but it failed in one-third of the patients who had the worst initial quality of life  |

**NOTE.** IV Ctri, intravenous ceftriaxone; SI, significant improvement.

**Table 3. Precedents for prolonged antibiotic therapy.**

| Disease                          | Organism                          | Treatment                        | Duration of treatment, months |
|----------------------------------|-----------------------------------|----------------------------------|-------------------------------|
| Drug-susceptible tuberculosis    | <i>Mycobacterium tuberculosis</i> | 2–4 antibiotics                  | 6–9                           |
| Multidrug-resistant tuberculosis | <i>M. tuberculosis</i>            | 3–5 antibiotics                  | 18–24                         |
| Leprosy                          | <i>Mycobacterium leprae</i>       | 3–4 antibiotics                  | 24                            |
| Atypical tuberculosis            | <i>Mycobacterium chelonae</i>     | Oral and intravenous antibiotics | 6–12                          |
| Q fever endocarditis             | <i>Coxiella burnetii</i>          | 2 antibiotics                    | 36                            |

**NOTE.** Data are based on [143–147].

year period. She received 12 months of intravenous antibiotic treatment, followed by 11 months of oral antibiotics, and her condition improved significantly [95]. Thus, this case report suggests that longer treatment may be beneficial in some patients with Lyme disease. Taken as a whole, these studies provide “credible scientific evidence” for persistence of *B. burgdorferi* infection after “adequate” short-term antibiotic treatment in humans.

That brings up the next question: does longer antibiotic treatment help in persistent Lyme disease? There have been a number of uncontrolled trials that support longer treatment of persistent disease symptoms [97–100]. The largest study included 277 patients who were treated with tetracycline for 1–11 months (mean duration, 4 months). The study showed that, after 2 months of therapy, 33% of patients had improvement in symptoms, but after 3 months of treatment, 61% of patients had decreased symptoms [97]. So this study suggests that longer treatment may result in better symptom outcome in Lyme disease. There have been other small, uncontrolled trials showing that longer treatment may have better symptom outcomes in patients with Lyme disease, including one trial that showed that patients who were re-treated with intravenous therapy had the greatest improvement in their symptoms [98–100].

In contrast to these uncontrolled trials, 2 randomized, placebo-controlled trials examined re-treatment of patients with persistent symptoms of Lyme disease (table 2) [101, 102]. Krupp et al. [102] studied 1 month of intravenous ceftriaxone, whereas Klempner et al. [101] studied 1 month of intravenous ceftriaxone followed by 2 months of oral doxycycline. The Krupp study showed improvement in fatigue with its 30-day treatment regimen, whereas the Klempner study showed no improvement in quality of life following re-treatment for 90 days. The main problem with these studies is that they included patients who had been symptomatic for an average of 4–5 years, and treatment with 1 month of intravenous antibiotics, with or without low-dose doxycycline, is insufficient for patients who have been sick this long [103, 104]. Thus, the generalizability of results in these highly selected patients with persistent Lyme disease is questionable [104].

In contrast to these studies, 2 placebo-controlled trials were presented in 2005 at the Columbia/Lyme Disease Association’s

annual meeting (table 2) [105, 106]. One study involved oral amoxicillin for 3 months versus placebo for previously treated patients, and re-treatment was successful for the two-thirds of patients with the best initial quality of life. A second study administered intravenous ceftriaxone for 10 weeks to patients with persistent neurologic symptoms of Lyme disease, and these patients had significant cognitive improvement with this treatment. We look forward to publication of these 2 placebo-controlled trials, which show that longer courses of antibiotic therapy are useful in patients with persistent Lyme disease.

### COINFECTION WITH TICKBORNE AGENTS

In addition to infection with *B. burgdorferi*, tickborne coinfections are being recognized more frequently. If a patient is treated for Lyme disease and has symptoms that have persisted or worsened, the lack of improvement may be due to the presence of *Babesia*, *Anaplasma*, *Ehrlichia*, or *Bartonella* coinfection [107–126]. Coinfection with *Babesia* and *Ehrlichia* has been shown to exacerbate Lyme disease in mouse models [108–110] and also in humans [111–118]. Traditionally, *Babesia*, *Anaplasma*, *Ehrlichia* and *Bartonella* are thought to produce acute fulminant infections, but in fact these pathogens may cause low-grade infections that can increase the severity and duration of Lyme disease [119–125].

A disturbing study from New Jersey examined the prevalence of coinfections in *Ixodes* ticks that transmit Lyme disease [126]. In that study, the prevalence of *B. burgdorferi* infection was 33.6%, but the prevalence of *Bartonella* infection was 34.5%. Thus, *Bartonella* species were found more often than the Lyme spirochete in these ticks. This observation presages a greater problem with *Bartonella* infection associated with tick exposure in the near future.

### TREATMENT APPROACH TO CHRONIC LYME DISEASE

What is the approach for a patient who presents with persistent symptoms of Lyme disease [127–140]? First, the Lyme Western blot should be repeated, and coinfection testing should be performed by a laboratory that is proficient in tickborne disease analysis. At the same time, other medical problems that could

cause persistent symptoms should be ruled out. Measurement of the CD57 natural killer cell level, which is an immunologic marker that can be used to monitor treatment in chronic Lyme disease, should be performed [129–131]. If neurologic symptoms are severe, a single-photon emission CT SPECT brain scan should be obtained, to see how much inflammation is present in the brain. Neuropsychiatric evaluation may also be helpful [132].

On the basis of these results, coinfections should be treated first, if any are present, and then oral or parenteral antibiotics should be used to treat symptoms of persistent Lyme disease. Antibiotic therapy should be administered in a rotating and open-ended manner, in conjunction with probiotics, to minimize adverse effects [133–136]. Monitoring of clinical symptoms, CD57 natural killer cell levels, and markers of inflammation should be performed in conjunction with treatment [137–140].

This approach differs from the recommendations of the current IDSA guidelines, which do not recognize persistent infection in chronic Lyme disease [141]. However, the treatment approach is consistent with the guidelines of the International Lyme and Associated Diseases Society, which mandates treatment for persistent infection in patients with chronic Lyme disease symptoms [142]. It is helpful to recall that *B. burgdorferi* shares certain pathophysiological features with mycobacterial infection and other chronic infections (table 1), that these infections may require prolonged antibiotic therapy (6–36 months), and that the risks of long-term treatment are considered justifiable in those situations (table 3) [143–147]. On the basis of the foregoing discussion, prolonged antibiotic therapy appears to be useful and justifiable in chronic Lyme disease.

In summary, >18,000 scientific articles have been written about Lyme disease. Some of these articles focus on the complex pathophysiology of *B. burgdorferi*, whereas others highlight the clinical uncertainty surrounding tickborne disease. Because the optimal therapy for this complicated illness is still in doubt, we must keep an open mind about the treatment of patients who present with persistent symptoms of Lyme and associated tickborne diseases.

## Acknowledgments

This article is dedicated to the memory of Dr. Paul Lavoie and Billi Goldberg.

I thank Drs. Robert Bransfield, David Dorward, Brian Fallon, Andrea Gaito, Julie Gerberding, Nick Harris, William Harvey, Barbara Johnson, Pat Joseph, Anne Kjemtrup, Robert Lane, Kenneth Liegner, Robert Lull, Alan MacDonald, David Martz, Daniel Moore, Scott Morrow, Steven Phillips, Walter Prehn, James Schaller, Virginia Sherr, Harold Smith, and Edward Winger for helpful discussion. I also thank Pat Smith of the Lyme Disease Association; Barb Barsocchini, Lorraine Johnson, Peggy Leonard, Lee Lull, Phyllis Mervine, and Ginger Savely of the California Lyme Disease Association; and Karen Forschner of the Lyme Disease Foundation for continuing support.

**Potential conflicts of interest.** R.B.S. is a consultant for QMedRX.

## References

1. Stricker RB, Lautin A, Burrascano JJ. Lyme disease: point/counterpoint. *Expert Rev Anti Infect Ther* **2005**; 3:155–65.
2. Johnson L, Stricker RB. Treatment of Lyme disease: a medicolegal assessment. *Expert Rev Anti Infect Ther* **2004**; 2:533–57.
3. Harvey WT, Salvato P. 'Lyme disease': ancient engine of an unrecognized borreliosis pandemic? *Med Hypotheses* **2003**; 60:742–59.
4. Lautin A, McNeil EL, Liegner KB, Stricker RB, Sigal LH. Lyme disease controversy: use and misuse of language. *Ann Intern Med* **2002**; 137:775–7.
5. Stricker RB, Phillips SE. Lyme disease without erythema migrans: cause for concern? *Am J Med* **2003**; 115:72.
6. Edlow JA. Erythema migrans. *Med Clin North Am* **2002**; 86:239–60.
7. Meek JI, Roberts CL, Smith EV, Cartter ML. Underreporting of Lyme disease by Connecticut physicians, 1992. *J Public Health Manag Pract* **1996**; 2:61–5.
8. Boltri JM, Hash RB, Vogel RL. Patterns of Lyme disease diagnosis and treatment by family physicians in a southeastern state. *J Community Health* **2002**; 27:395–402.
9. Porcella SF, Schwan TG. *Borrelia burgdorferi* and *Treponema pallidum*: a comparison of functional genomics, environmental adaptations, and pathogenic mechanisms. *J Clin Invest* **2001**; 107:651–6.
10. Casjens S, Palmer N, van Vugt R, et al. A bacterial genome in flux: the twelve linear and nine circular extrachromosomal DNAs in an infectious isolate of the Lyme disease spirochete *Borrelia burgdorferi*. *Mol Microbiol* **2000**; 35:490–516.
11. Schoeler GB, Wikel SK. Modulation of host immunity by haematophagous arthropods. *Ann Trop Med Parasitol* **2001**; 95:755–71.
12. Hänni S, Liversidge J, Sternberg JM, Bowman AS. *Ixodes ricinus* tick salivary gland extract inhibits IL-10 secretion and CD69 expression by mitogen-stimulated murine splenocytes and induces hyporesponsiveness in B lymphocytes. *Parasite Immunol* **2003**; 25:27–37.
13. Ramamoorthi N, Narasimhan S, Pal U, et al. The Lyme disease agent exploits a tick protein to infect the mammalian host. *Nature* **2005**; 436:573–7.
14. Rhen M, Eriksson S, Clements M, Bergstrom S, Normark SJ. The basis of persistent bacterial infections. *Trends Microbiol* **2003**; 11:80–6.
15. Liang FT, Jacobs MB, Bowers LC, Philipp MT. An immune evasion mechanism for spirochetal persistence in Lyme borreliosis. *J Exp Med* **2002**; 195:415–22.
16. Guner ES. Complement evasion by the Lyme disease spirochete *Borrelia burgdorferi* grown in host-derived tissue co-cultures: role of fibronectin in complement-resistance. *Experientia* **1996**; 52:364–72.
17. Kraiczy P, Hellwege J, Skerka C, et al. Complement resistance of *Borrelia burgdorferi* correlates with expression of BbCRASP-1, a novel linear plasmid-encoded surface protein that interacts with human factor H and FHL-1 and is unrelated to Erp proteins. *J Biol Chem* **2004**; 279:2421–9.
18. Zhang H, Raji A, Theisen M, Hansen PR, Marconi RT. bdrF2 of Lyme disease spirochetes is coexpressed with a series of cytoplasmic proteins and is produced specifically during early infection. *J Bacteriol* **2005**; 187:175–84.
19. Liang FT, Brown EL, Wang T, Iozzo RV, Fikrig E. Protective niche for *Borrelia burgdorferi* to evade humoral immunity. *Am J Pathol* **2004**; 165:977–85.
20. Liang FT, Yan J, Mbow ML, et al. *Borrelia burgdorferi* changes its surface antigenic expression in response to host immune responses. *Infect Immun* **2004**; 72:5759–67.
21. Qiu WG, Schutzer SE, Bruno JF, et al. Genetic exchange and plasmid transfers in *Borrelia burgdorferi* sensu stricto revealed by three-way genome comparisons and multilocus sequence typing. *Proc Natl Acad Sci U S A* **2004**; 101:14150–5.
22. Stewart PE, Hoff J, Fischer E, Krum JG, Rosa PA. Genome-wide transposon mutagenesis of *Borrelia burgdorferi* for identification of phenotypic mutants. *Appl Environ Microbiol* **2004**; 70:5973–9.
23. Grimm D, Eggers CH, Caimano MJ, et al. Experimental assessment

- of the roles of linear plasmids lp25 and lp28-1 of *Borrelia burgdorferi* throughout the infectious cycle. *Infect Immun* **2004**;72:5938–46.
24. Bruck DK, Talbot ML, Cluss RG, Boothby JT. Ultrastructural characterization of the stages of spheroplast preparation of *Borrelia burgdorferi*. *J Microbiol Methods* **1995**;23:219–28.
  25. Preac-Mursic V, Wanner G, Reinhardt S, Wilske B, Busch U, Marget W. Formation and cultivation of *Borrelia burgdorferi* spheroplast L-form variants. *Infection* **1996**;24:218–26.
  26. Alban PS, Johnson PW, Nelson DR. Serum-starvation-induced changes in protein synthesis and morphology of *Borrelia burgdorferi*. *Microbiology* **2000**;146:119–27.
  27. Brorson O, Brorson SH. A rapid method for generating cystic forms of *Borrelia burgdorferi*, and their reversal to mobile spirochetes. *APMIS* **1998**;106:1131–41.
  28. Brorson O, Brorson SH. An in vitro study of the susceptibility of mobile and cystic forms of *Borrelia burgdorferi* to metronidazole. *APMIS* **1999**;107:566–76.
  29. Kersten A, Poitschek C, Rauch S, Aberer E. Effects of penicillin, ceftriaxone, and doxycycline on the morphology of *Borrelia burgdorferi*. *Antimicrob Agents Chemother* **1995**;39:1127–33.
  30. Montgomery RR, Schreck K, Wang X, Malawista SE. Human neutrophil calprotectin reduces the susceptibility of *Borrelia burgdorferi* to penicillin. *Infect Immun* **2006**;74:2468–72.
  31. Terekhova D, Sartakova ML, Wormser GP, Schwartz I, Cabello FC. Erythromycin resistance in *Borrelia burgdorferi*. *Antimicrob Agents Chemother* **2002**;46:3637–40.
  32. Galbraith KM, Ng AC, Eggers BJ, Kuchel CR, Eggers CH, Samuels DS. parC mutations in fluoroquinolone-resistant *Borrelia burgdorferi*. *Antimicrob Agents Chemother* **2005**;49:4354–7.
  33. Criswell D, Tobiason VL, Lodmell JS, Samuels DS. Mutations conferring aminoglycoside and spectinomycin resistance in *Borrelia burgdorferi*. *Antimicrob Agents Chemother* **2006**;50:445–52.
  34. Grab DJ, Perides G, Dumler JS, et al. *Borrelia burgdorferi*, host-derived proteases, and the blood-brain barrier. *Infect Immun* **2005**;73:1014–22.
  35. Ma Y, Sturrock A, Weis JJ. Intracellular localization of *Borrelia burgdorferi* within human endothelial cells. *Infect Immun* **1991**;59:671–8.
  36. Klempner MS, Noring R, Rogers RA. Invasion of human skin fibroblasts by the Lyme disease spirochete, *Borrelia burgdorferi*. *J Infect Dis* **1993**;167:1074–81.
  37. Girschick HJ, Huppertz HI, Russmann H, Krenn V, Karch H. Intracellular persistence of *Borrelia burgdorferi* in human synovial cells. *Rheumatol Int* **1996**;16:125–30.
  38. Linder S, Heimerl C, Fingerle V, Aepfelbacher M, Wilske B. Coiling phagocytosis of *Borrelia burgdorferi* by primary human macrophages is controlled by CDC42Hs and Rac1 and involves recruitment of Wiskott-Aldrich syndrome protein and Arp2/3 complex. *Infect Immun* **2001**;69:1739–46.
  39. Georgilis K, Peacocke M, Klempner MS. Fibroblasts protect the Lyme disease spirochete, *Borrelia burgdorferi*, from ceftriaxone in vitro. *J Infect Dis* **1992**;166:440–4.
  40. Brouqui P, Badiaga S, Raoult D. Eukaryotic cells protect *Borrelia burgdorferi* from the action of penicillin and ceftriaxone but not from the action of doxycycline and erythromycin. *Antimicrob Agents Chemother* **1996**;40:1552–4.
  41. Livengood JA, Gilmore RD. Invasion of human neuronal and glial cells by an infectious strain of *Borrelia burgdorferi*. *Microbes Infect* **2006**;8:2832–40.
  42. Aberer E, Koszik F, Silberer M. Why is chronic Lyme borreliosis chronic? *Clin Infect Dis* **1997**;25(Suppl 1):S64–70.
  43. Embers ME, Ramamoorthy R, Philipp MT. Survival strategies of *Borrelia burgdorferi*, the etiologic agent of Lyme disease. *Microbes Infect* **2004**;6:312–8.
  44. Williams LR, Austin FE. Hemolytic activity of *Borrelia burgdorferi*. *Infect Immun* **1992**;60:3224–30.
  45. Cluss RG, Silverman DA, Stafford TR. Extracellular secretion of the *Borrelia burgdorferi* Oms28 porin and Bgp, a glycosaminoglycan binding protein. *Infect Immun* **2004**;72:6279–86.
  46. Stevenson B, von Lackum K, Wattier RL, McAlister JD, Miller JC, Babb K. Quorum sensing by the Lyme disease spirochete. *Microbes Infect* **2003**;5:991–7.
  47. Babb K, von Lackum K, Wattier RL, Riley SP, Stevenson B. Synthesis of autoinducer 2 by the Lyme disease spirochete, *Borrelia burgdorferi*. *J Bacteriol* **2005**;187:3079–87.
  48. Von Lackum K, Babb K, Riley SP, Wattier RL, Bykowski T, Stevenson B. Functionality of *Borrelia burgdorferi* LuxS: the Lyme disease spirochete produces and responds to the pheromone autoinducer-2 and lacks a complete activated-methyl cycle. *Int J Med Microbiol* **2006**;296(Suppl 40):92–102.
  49. Chan J, Flynn J. The immunological aspects of latency in tuberculosis. *Clin Immunol* **2004**;110:2–12.
  50. Mukamolova GV, Turapov OA, Young DI, Kaprelyants AS, Kell DB, Young M. A family of autocrine growth factors in *Mycobacterium tuberculosis*. *Mol Microbiol* **2002**;46:623–35.
  51. Behera AK, Hildebrand E, Szafrański J, et al. Role of aggrecanase 1 in Lyme arthritis. *Arthritis Rheum* **2006**;54:3319–29.
  52. Bakken LK, Case KL, Callister SM, Bourdeau NJ, Schell RF. Performance of 45 laboratories participating in a proficiency testing program for Lyme disease serology. *JAMA* **1992**;268:891–5.
  53. Brown SL, Hanson SL, Langone JJ. Role of serology in the diagnosis of Lyme disease. *JAMA* **1999**;282:62–6.
  54. Ekerfelt C, Ernerudh J, Forsberg P, et al. Lyme borreliosis in Sweden—diagnostic performance of five commercial *Borrelia* serology kits using sera from well-defined patient groups. *APMIS* **2004**;112:74–8.
  55. Ma B, Christen B, Leung D, Vigo-Pelfrey C. Serodiagnosis of Lyme borreliosis by Western immunoblot: reactivity of various significant antibodies against *Borrelia burgdorferi*. *J Clin Microbiol* **1992**;30:370–6.
  56. Feder HM Jr, Gerber MA, Luger SW, Ryan RW. Persistence of serum antibodies to *Borrelia burgdorferi* in patients treated for Lyme disease. *Clin Infect Dis* **1992**;15:788–93.
  57. Engstrom SM, Shoop E, Johnson RC. Immunoblot interpretation criteria for serodiagnosis of early Lyme disease. *J Clin Microbiol* **1995**;33:419–27.
  58. Ledue TB, Collins MF, Craig WY. New laboratory guidelines for serologic diagnosis of Lyme disease: evaluation of the two-test protocol. *J Clin Microbiol* **1996**;34:2343–50.
  59. Trevejo RT, Krause PJ, Sikand VK, et al. Evaluation of two-test serodiagnostic method for early Lyme disease in clinical practice. *J Infect Dis* **1999**;179:931–8.
  60. Hilton E, Devoti J, Sood S. Recommendation to include OspA and OspB in the new immunoblotting criteria for serodiagnosis of Lyme disease. *J Clin Microbiol* **1996**;34:1353–4.
  61. Dumler JS. Molecular diagnosis of Lyme disease: review and meta-analysis. *Mol Diagn* **2001**;6:1–11.
  62. Van Dam AP. Recent advances in the diagnosis of Lyme disease. *Expert Rev Mol Diagn* **2001**;1:413–27.
  63. Aguero-Rosenfeld ME, Wang G, Schwartz I, Wormser GP. Diagnosis of Lyme borreliosis. *Clin Microbiol Rev* **2005**;18:484–509.
  64. DePietropaolo DL, Powers JH, Gill JM, Foy AJ. Diagnosis of Lyme disease. *Am Fam Physician* **2005**;72:297–304.
  65. Preac-Mursic V, Weber K, Pfister HW, et al. Survival of *Borrelia burgdorferi* in antibiotic-treated patients with Lyme borreliosis. *Infection* **1989**;17:355–9.
  66. Wormser GP, Dattwyler RJ. Lyme disease: myths and reality. *New York Times*. 9 June 2006.
  67. Montgomery RR, Nathanson MH, Malawista SE. The fate of *Borrelia burgdorferi*, the agent for Lyme disease, in mouse macrophages: destruction, survival, recovery. *J Immunol* **1993**;150:909–15.
  68. Bockenstedt LK, Mao J, Hodzic E, Barthold SW, Fish D. Detection of attenuated, noninfectious spirochetes in *Borrelia burgdorferi*-infected mice after antibiotic treatment. *J Infect Dis* **2002**;186:1430–7.

69. Straubinger RK, Summers BA, Chang YF, Appel MJ. Persistence of *Borrelia burgdorferi* in experimentally infected dogs after antibiotic treatment. *J Clin Microbiol* **1997**; 35:111–6.
70. Straubinger RK. PCR-based quantification of *Borrelia burgdorferi* organisms in canine tissues over a 500-day postinfection period. *J Clin Microbiol* **2000**; 38:2191–9.
71. Cadavid D, O'Neill T, Schaefer H, Pachner AR. Localization of *Borrelia burgdorferi* in the nervous system and other organs in a nonhuman primate model of Lyme disease. *Lab Invest* **2000**; 80:1043–54.
72. Pachner AR, Cadavid D, Shu G, et al. Central and peripheral nervous system infection, immunity, and inflammation in the NHP model of Lyme borreliosis. *Ann Neurol* **2001**; 50:330–8.
73. Pachner AR, Dail D, Narayan K, Dutta K, Cadavid D. Increased expression of B-lymphocyte chemoattractant, but not pro-inflammatory cytokines, in muscle tissue in rhesus chronic Lyme borreliosis. *Cytokine* **2002**; 19:297–307.
74. Cadavid D, Bai Y, Hodzic E, Narayan K, Barthold SW, Pachner AR. Cardiac involvement in non-human primates infected with the Lyme disease spirochete *Borrelia burgdorferi*. *Lab Invest* **2004**; 84:1439–50.
75. Miller JC, Narayan K, Stevenson B, Pachner AR. Expression of *Borrelia burgdorferi* *erp* genes during infection of non-human primates. *Microb Pathog* **2005**; 39:27–33.
76. Nocton JJ, Dressler F, Rutledge BJ, Rys PN, Persing DH, Steere AC. Detection of *Borrelia burgdorferi* DNA by polymerase chain reaction in synovial fluid in Lyme arthritis. *N Engl J Med* **1994**; 330:229–34.
77. Nocton JJ, Bloom BJ, Rutledge BJ, et al. Detection of *Borrelia burgdorferi* DNA by polymerase chain reaction in cerebrospinal fluid in patients with Lyme neuroborreliosis. *J Infect Dis* **1996**; 174:623–7.
78. Lawrence C, Lipton RB, Lowy FD, Coyle PK. Seronegative chronic relapsing neuroborreliosis. *Eur Neurol* **1995**; 35:113–7.
79. Fraser DD, Kong LI, Miller FW. Molecular detection of persistent *Borrelia burgdorferi* in a man with dermatomyositis. *Clin Exp Rheumatol* **1992**; 10:387–90.
80. Berglund J, Stjernberg L, Ornstein K, Tykesson-Joelsson K, Walter H. Five-year follow-up study of patients with neuroborreliosis. *Scand J Infect Dis* **2002**; 34:421–5.
81. Shadick NA, Phillips CB, Sangha O, et al. Musculoskeletal and neurologic outcomes in patients with previously treated Lyme disease. *Ann Intern Med* **1999**; 131:919–26.
82. Treib JA, Fernandez A, Haass A, Grauer MR, Holzer G, Woessner R. Clinical and serologic follow-up in patients with neuroborreliosis. *Neurology* **1998**; 51:1489–91.
83. Valesova H, Mailer J, Havlik J, Hulinska D, Hercogova J. Long-term results in patients with Lyme arthritis following treatment with ceftriaxone. *Infection* **1996**; 24:98–102.
84. Shadick NA, Phillips CD, Logigian EL, et al. The long-term clinical outcomes of Lyme disease. A population-based retrospective cohort study. *Ann Intern Med* **1994**; 121:560–7.
85. Asch ES, Bujak DI, Weiss M, Peterson MG, Weinstein A. Lyme disease: an infectious and postinfectious syndrome. *J Rheumatol* **1994**; 21:454–61.
86. Pfister HW, Preac-Mursic V, Wilske B, Schielke E, Sorgel F, Einhaupl KM. Randomized comparison of ceftriaxone and cefotaxime in Lyme neuroborreliosis. *J Infect Dis* **1991**; 163:311–8.
87. Logigian EL, Kaplan RF, Steere AC. Chronic neurologic manifestations of Lyme disease. *N Engl J Med* **1990**; 323:1438–44.
88. Breier F, Khanakah G, Stanek G, et al. Isolation and polymerase chain reaction typing of *Borrelia afzelii* from a skin lesion in a seronegative patient with generalized bullous lichen sclerosus et atrophicus. *Br J Dermatol* **2001**; 144:387–92.
89. Oksi J, Marjamaki M, Nikoskelainen J, Viljanen MK. *Borrelia burgdorferi* detected by culture and PCR in clinical relapse of disseminated Lyme borreliosis. *Ann Med* **1999**; 31:225–32.
90. Bayer ME, Zhang L, Bayer MH. *Borrelia burgdorferi* DNA in the urine of treated patients with chronic Lyme disease symptoms: a PCR study of 97 cases. *Infection* **1996**; 24:347–53.
91. Priem S, Burmester GR, Kamradt T, Wolbart K, Rittig MG, Krause A. Detection of *Borrelia burgdorferi* by polymerase chain reaction in synovial membrane, but not in synovial fluid from patients with persisting Lyme arthritis after antibiotic therapy. *Ann Rheum Dis* **1998**; 57:118–21.
92. Battafarano DF, Combs JA, Enzenauer RJ, Fitzpatrick JE. Chronic septic arthritis caused by *Borrelia burgdorferi*. *Clin Orthop* **1993**; 297:238–41.
93. Preac-Mursic V, Pfister HW, Spiegel H, et al. First isolation of *Borrelia burgdorferi* from an iris biopsy. *J Clin Neuroophthalmol* **1993**; 13:155–61.
94. Petrovic M, Vogelaers D, Van Renterghem L, Carton D, De Reuck J, Afschrift M. Lyme borreliosis—a review of the late stages and treatment of four cases. *Acta Clin Belg* **1998**; 53:178–83.
95. Ferris i Tortajada J, Lopez Andreu JA, Salcedo Vivo J, Sala Lizarraga JV. Lyme borreliosis. *Lancet* **1995**; 345:1436–7.
96. Frey M, Jaulhac B, Piemont Y, et al. Detection of *Borrelia burgdorferi* DNA in muscle of patients with chronic myalgia related to Lyme disease. *Am J Med* **1998**; 104:591–4.
97. Donta ST. Tetracycline therapy for chronic Lyme disease. *Clin Infect Dis* **1997**; 25(Suppl 1):S52–6.
98. Oksi J, Nikoskelainen J, Viljanen MK. Comparison of oral cefixime and intravenous ceftriaxone followed by oral amoxicillin in disseminated Lyme borreliosis. *Eur J Clin Microbiol Infect Dis* **1998**; 17:715–9.
99. Wahlberg P, Granlund H, Nyman D, Panelius J, Seppala I. Treatment of late Lyme borreliosis. *J Infect* **1994**; 29:255–61.
100. Fallon BA. Repeated antibiotic treatment in chronic Lyme disease. *J Spiro Tick Dis* **1999**; 6:94–101.
101. Klemmner MS, Hu LT, Evans J, et al. Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. *N Engl J Med* **2001**; 345:85–92.
102. Krupp LB, Hyman LG, Grimson R, et al. Study and treatment of post Lyme disease (STOP-LD): a randomized double masked clinical trial. *Neurology* **2003**; 60:1923–30.
103. Bransfield R, Brand S, Sherr V. Treatment of patients with persistent symptoms and a history of Lyme disease. *N Engl J Med* **2001**; 345:1424–5.
104. Cameron DJ. Generalizability in two clinical trials of Lyme disease. *Epidemiol Perspect Innov* **2006**; 3:12–18.
105. Fallon BA. Preliminary results of Columbia controlled Lyme treatment study. In: Program and abstracts of the Columbia University/LDA Conference, Lyme & Other Tick-Borne Diseases: Emerging Tick-Borne Diseases (Philadelphia). **2005**:M1.
106. Cameron DJ. Results from Lyme disease treatment trial. In: Program and abstracts of the Columbia University/LDA Conference, Lyme & Other Tick-Borne Diseases: Emerging Tick-Borne Diseases (Philadelphia). **2005**:L1.
107. Stricker RB. Lyme disease: a potential polymicrobial infection. *ASM News* **2003**; 69:265.
108. Thomas V, Anguita J, Barthold SW, Fikrig E. Coinfection with *Borrelia burgdorferi* and the agent of human granulocytic ehrlichiosis alters murine immune responses, pathogen burden, and severity of Lyme arthritis. *Infect Immun* **2001**; 69:3359–71.
109. Zeidner NS, Dolan MC, Massung R, Piesman J, Fish D. Coinfection with *Borrelia burgdorferi* and the agent of human granulocytic ehrlichiosis suppresses IL-2 and IFN gamma production and promotes an IL-4 response in C3H/HeJ mice. *Parasite Immunol* **2000**; 22:581–8.
110. Moro MH, Zegarra-Moro OL, Bjornsson J, et al. Increased arthritis severity in mice coinfecting with *Borrelia burgdorferi* and *Babesia microti*. *J Infect Dis* **2002**; 186:428–31.
111. Benach JL, Coleman JL, Habicht GS, MacDonald A, Grunwaldt E, Giron JA. Serological evidence for simultaneous occurrences of Lyme disease and babesiosis. *J Infect Dis* **1985**; 152:473–7.
112. Marcus LC, Steere AC, Duray PH, Anderson AE, Mahoney EB. Fatal pancarditis in a patient with coexistent Lyme disease and babesiosis:



- demonstration of spirochetes in the myocardium. *Ann Intern Med* **1985**; 103:374–6.
113. Nadelman RB, Horowitz HW, Hsieh TC, et al. Simultaneous human granulocytic ehrlichiosis and Lyme borreliosis. *N Engl J Med* **1997**; 337:27–30.
  114. DeMartino SJ, Carlyon JA, Fikrig E. Coinfections with *Borrelia burgdorferi* and the agent of human granulocytic ehrlichiosis. *N Engl J Med* **2001**; 345:150–1.
  115. Krause PJ, McKay K, Thompson CA, et al. Disease-specific diagnosis of coinfecting tickborne zoonoses: babesiosis, human granulocytic ehrlichiosis, and Lyme disease. *Clin Infect Dis* **2002**; 34:1184–91.
  116. Stricker RB, Harris NS, Yong DC, Winger EE. Clinical and seroepidemiologic characteristics of *Babesia* WA-1 coinfection in patients with Lyme disease in California. *J Invest Med* **2003**; 51(Suppl 1):S145.
  117. Eskow E, Rao RV, Mordechai E. Concurrent infection of the central nervous system by *Borrelia burgdorferi* and *Bartonella henselae*: evidence for a novel tick-borne disease complex. *Arch Neurol* **2001**; 58: 1357–63.
  118. Holden K, Boothby JT, Anand S, Massung RF. Detection of *Borrelia burgdorferi*, *Ehrlichia chafeensis*, and *Anaplasma phagocytophilum* in ticks (Acari: Ixodidae) from a coastal region of California. *J Med Entomol* **2003**; 40:534–9.
  119. Krause PJ, Telford SR, Spielman A, et al. Concurrent Lyme disease and babesiosis: evidence for increased severity and duration of illness. *JAMA* **1996**; 275:1657–60.
  120. Oleson CV, Sivalingam JJ, O'Neill BJ, Staas WE. Transverse myelitis secondary to coexistent Lyme disease and babesiosis. *J Spinal Cord Med* **2003**; 26:168–71.
  121. Krause PJ, Spielman A, Telford SR, et al. Persistent parasitemia after acute babesiosis. *N Engl J Med* **1998**; 339:160–5.
  122. Alfred DR. Babesiosis: persistence in the face of adversity. *Trends Parasitol* **2003**; 19:51–5.
  123. Harrus S, Waner T, Aizenberg I, Foley JE, Poland AM, Bark H. Amplification of ehrlichial DNA from dogs 34 months after infection with *Ehrlichia canis*. *J Clin Microbiol* **1998**; 36:73–6.
  124. Dumler JS, Bakken JS. Human granulocytic ehrlichiosis in Wisconsin and Minnesota: a frequent infection with the potential for persistence. *J Infect Dis* **1996**; 173:1027–30.
  125. Chomel BB, Kasten RW, Sykes JE, Boulouis HJ, Breitschwerdt EB. Clinical impact of persistent *Bartonella* bacteremia in humans and animals. *Ann N Y Acad Sci* **2003**; 990:267–78.
  126. Adelson ME, Rao RV, Tilton RC, et al. Prevalence of *Borrelia burgdorferi*, *Bartonella* spp., *Babesia microti*, and *Anaplasma phagocytophila* in *Ixodes scapularis* ticks collected in Northern New Jersey. *J Clin Microbiol* **2004**; 42:2799–801.
  127. Burrascano JJ. Lyme disease. In: Rakei RE, ed. *Conn's current therapy*. Philadelphia: WB Saunders Company, **1997**:140–3.
  128. Liegner KB, Kochevar J. Guidelines for the clinical diagnosis of Lyme disease. *Ann Intern Med* **1998**; 129:422–3.
  129. Stricker RB, Winger EE. Decreased CD57 lymphocyte subset in patients with chronic Lyme disease. *Immunol Lett* **2001**; 76:43–48.
  130. Stricker RB, Burrascano J, Winger EE. Longterm decrease in the CD57 lymphocyte subset in a patient with chronic Lyme disease. *Ann Agric Environ Med* **2002**; 9:111–3.
  131. Stricker RB, Winger EE. Normalization of the CD57 natural killer cell subset associated with prolonged antibiotic therapy in patients with chronic Lyme disease. *Clin Immunol* **2002**; 103:S117–8.
  132. Fallon BA, Das S, Plutchok JJ, Tager F, Liegner K, Van Heertum R. Functional brain imaging and neuropsychological testing in Lyme disease. *Clin Infect Dis* **1997**; 25(Suppl 1):S57–63.
  133. Brorson O, Brorson SH. An in vitro study of the susceptibility of mobile and cystic forms of *Borrelia burgdorferi* to tinidazole. *Int Microbiol* **2004**; 7:139–42.
  134. Hunfeld KP, Wichelhaus TA, Rodel R, Acker G, Brade V, Kraiczky P. Comparison of in vitro activities of ketolides, macrolides, and an azalide against the spirochete *Borrelia burgdorferi*. *Antimicrob Agents Chemother* **2004**; 48:344–7.
  135. Stricker RB, Thomas SL, Moore DH, Winger EE. Efficacy of clarithromycin/cefdinir combination therapy in patients with chronic Lyme disease. *J Invest Med* **2005**; 53:S156.
  136. D'Souza AL, Rajkumar C, Cooke J, Bulpitt CJ. Probiotics in prevention of antibiotic associated diarrhoea: meta-analysis. *BMJ* **2002**; 324: 1361–6.
  137. Widhe M, Grusell M, Ekerfelt C, et al. Cytokines in Lyme borreliosis: lack of early TNF-alpha and TGF-beta 1 responses are associated with chronic neuroborreliosis. *Immunology* **2002**; 107:46–55.
  138. Widhe M, Jarefors S, Ekerfelt C, et al. *Borrelia* specific IFN-gamma and IL-4 secretion in blood and CSF during the course of human Lyme borreliosis: relation to clinical outcome. *J Infect Dis* **2004**; 189: 1881–1891.
  139. Liegner KB, Duray P, Agricola M, et al. Lyme disease and the clinical spectrum of antibiotic responsive chronic meningoencephalomyelitides. *J Spiro Tick Dis* **1997**; 4:61–73.
  140. Stricker RB, McNeil EL. Duration of antibiotic therapy for Lyme disease. *Ann Intern Med* **2004**; 140:W6.
  141. Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* **2006**; 43:1089–134.
  142. Cameron D, Gaito A, Harris N, et al. Evidence-based guidelines for the management of Lyme disease. *Expert Rev Anti Infect Ther* **2004**; 2(1 Suppl):S1–13.
  143. Small PM, Fujiwara PI. Management of tuberculosis in the United States. *N Engl J Med* **2001**; 345:189–200.
  144. Van Helden PD, Donald PR, Victor TC, et al. Antimicrobial resistance in tuberculosis: an international perspective. *Expert Rev Anti Infect Ther* **2006**; 4:759–66.
  145. Shaw IN, Christian M, Jesudasan K, Kurian N, Rao GS. Effectiveness of multidrug therapy in multibacillary leprosy: a long-term follow-up of 34 multibacillary leprosy patients treated with multidrug regimens till skin smear negativity. *Lepr Rev* **2003**; 74:141–7.
  146. Wallace RJ Jr, Tanner D, Brennan PJ, Brown BA. Clinical trial of clarithromycin for cutaneous (disseminated) infection due to *Mycobacterium chelonae*. *Ann Intern Med* **1993**; 119:482–6.
  147. Rolain JM, Mallet MN, Raoult D. Correlation between serum doxycycline concentrations and serologic evolution in patients with *Coxiella burnetii* endocarditis. *J Infect Dis* **2003**; 188:1322–5.