

Lyme Disease - A Clear and Present Danger

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Lyme disease or Lyme borreliosis is the most common tick-borne disease in the northern hemisphere (North America, Europe, and Asia) with more than 20,000 new cases being reported annually in the U.S. alone, according to the Centers for Disease Control and Prevention (CDC). While Lyme disease has been found in nearly all of the fifty states, it is considered endemic in the northeast (Maine to Virginia), the upper midwest (Wisconsin and Minnesota), and the Pacific coast (Oregon, northern California and parts of Nevada, Arizona, and Utah). Rarely fatal, Lyme disease is a major concern because it is difficult to diagnose and delayed or inadequate treatment can lead to extremely serious, difficult to treat, and disabling consequences. It is caused by the bite of a tick infected with *Borrelia burgdorferi* which is a spirochete form of bacterium that is similar to the organism that causes syphilis.

Lyme disease was first recognized in the United States in 1975 when Dr. Allen Steere, who was studying rheumatology at Yale University, was called in by Connecticut's chief epidemiologist to investigate a mysterious outbreak of juvenile rheumatoid arthritis in three small, rural communities — Lyme, Old Lyme, and East Haddam. Here was a "cluster" of individuals, 39 children and 12 adults, with a comparatively rare disease where statistically one might expect to see only a single occurrence. After interviewing the families to determine what they might have in common, Dr. Steere ruled out the nearby nuclear power plant, the drinking water, the local swimming pool, something that they had all eaten, or some communicable disease. Noting the rural setting, that most of the afflicted were children who lived and played near wooded areas, and that the onset of illness consistently came during the summer and early fall, it was concluded that the transmission of the disease might involve an arthropod vector (i.e., insects and ticks that transmit disease from one organism to another), much the way mosquitos are responsible for malaria and yellow fever, and ticks are responsible for Rocky Mountain spotted fever and tularemia. In the interviews, some patients recalled being bitten by a tick and others remembered a skin rash (erythema migrans or EM) which developed just prior to their arthritis symptoms. Steere recognized that the "bull's-eye" rash was a significant manifestation of the disease. A researcher from Europe, who was visit-

ing Yale, remarked that the rash was similar to a condition frequently encountered in northern Europe. Early in the 20th century, European researchers (Afzelius in Sweden and Lipschutz in Austria) had linked the northern European rash phenomenon to a tick bite. When it was learned that the rash was responsive to penicillin, it was evident that the rash was a consequence of a bacterium rather than a virus. Further, that the rash was usually found somewhere on the torso suggested a crawling vector rather than a flying one. What was previously named "Lyme Arthritis" was changed to "Lyme Disease."

It was not until 1982 that Dr. Willy Burgdorfer, at the Rocky Mountain Laboratory in Hamilton, Montana, isolated the spirochete cause of Lyme disease from the mid-gut of *Ixodes* ticks. In addition, Dr. Burgdorfer tested sera from patients with clinically diagnosed Lyme disease and found antibodies that reacted to the bacterium. The dots were beginning to connect, and a number of world wide syndromes dating back to colonial days were now linked to this newly identified spirochete bacterium.

Lyme Disease

Lyme disease has three stages. The first stage, or early localized stage, is characterized by the appearance of a "bull's-eye" type of skin rash (EM) and flu-like symptoms anywhere from three days to four weeks after the tick bite. Joint pain, muscle aches, depression, swollen lymph nodes, and severe fatigue are common. Fortunately, prompt treatment with an appropriate antibiotic is curative in the majority of cases. The second stage, or early disseminated stage, occurs when the bacterium slowly begins to disperse to multiple sites throughout the body via the blood stream. Symptoms include a recurrence of the rash (distant from the tick bite), facial or Bell's palsy, pain and swelling in the larger joints (particularly the knees), heart palpitations, meningitis, and dizziness. The third stage, or late disseminated stage, occurs months to years after the tick bite. The symptoms include chronic arthritis, fatigue, and neurological problems like numbness or tingling in the hands or feet, memory loss, mood changes — and in the most severe of cases — permanent paraplegia (paralysis of the lower part of the body).

As mentioned earlier, Lyme disease is difficult to diagnose. The symptoms are quite common and mimic many other diseases (e.g., "summer flu"). The symptoms are

not always neatly confined to their respective stages, not every symptom is experienced in every stage, the severity goes from relatively mild to conditions that require hospitalization, and the diagnostic tests are not 100% reliable.

Ticks

Worldwide, there are 850 species of ticks. There are hard ticks which possess a hardened dorsal shield and there are soft ticks which lack a dorsal shield. In the U.S., there are about eighty species of ticks, of which only about a dozen or so represent a major public health or veterinary concern. Of that dozen, only two hard ticks are related to Lyme disease: the blacklegged tick, *Ixodes scapularis*, (aka deer tick or bear tick) in the north-east and north central states (Fig. 1) — and the western blacklegged tick, *Ixodes pacificus*, on the pacific coast and parts of Nevada, Arizona, and Utah.

Ticks are not insects. They are grouped with spiders and mites, and are found around the world in warm, humid climates. Both males and females are obligate ectoparasites which means they are dependent upon and live on the exterior of the host organism (e.g., fleas and lice). They meet their nutritional needs by drawing blood from the host (hematophagy), which may be a mammal, a reptile, or a bird. In general, ticks have four stages: egg, larva (infant), nymph (immature), and adult (mature), and a two year life cycle which involves three hosts. Curiously, the larva has three pairs of legs, while the nymphs and adults have four pairs of legs. Ticks are most active during the spring and summer. They do not jump, fly, climb trees, or blow around in the wind. They frequent animal trails and perch at the top of grass blades or low growing bushes. They assume a “questing” pose where they cling to the vegetation with their hind legs and extend their front legs forward — waiting for a prospective meal to wander by — literally within



Photo CDC/James Gathary, William Nicholson

▲ Figure 2: This shows a female deer tick (*Ixodes scapularis*) “questing” for a host.

reach (Fig. 2). Once onboard a host, the tick may wander over the host for one to three hours before attaching and feeding. Ticks feed slowly and may remain attached to a host for several days. It’s during the feeding portion of the life cycle that the ticks either pick up the disease from an infected host — or they pass the infection on to an uninfected host. It often takes several hours of feeding before the disease organism is transmitted to the host, so that means that a tick bite does not necessarily guarantee an infection. Because the nymph is smaller (the size of a poppy seed) than the adult, it has the greater chance of going unnoticed, attaching, feeding, and successfully conveying the disease to a host.

Favorite reservoirs for *Ixodes scapularis* are the white-footed mouse (*Peromyscus leucopus*) and the white-tailed deer (*Odocoileus virginianus*) (Fig 3). In the west, *Ixodes pacificus* seems to favor the western fence lizard (*Sceloporus occidentalis*), the dusky-footed woodrat (*Neotoma fuscipes*), the deer mouse (*Peromyscus maniculatus*) and the black-tailed deer (aka mule deer, *Odocoileus hemionus*). Fifty-two mammals, forty-eight birds, and eight reptiles were identified as hosts for at least one stage of the tick life cycle. In other words, the tick is not limited when it comes to selecting a host.

Blacklegged Tick (*Ixodes scapularis*)



Photo CDC

▲ Figure 1: This shows the relative sizes of the respective life stages compared to a dime. The nymph and adult stages of the deer tick have been described as approximately the size of a poppy seed and a sesame seed respectively.

Borrelia burgdorferi

Borrelia burgdorferi is the causative agent of Lyme disease. The generic epithet is derived from Am’ed’ee Borrell (1870 - 1961), a famous French bacteriologist at the Pasteur Institute in Paris. The specific epithet comes from Willy Burgdorfer (1932 -), a Scientist Emeritus at



Photo William C. Miller III

▲ Figure 3: A beautiful, male, white-tailed deer (*Odocoileus virginianus*) sampling a neighbor's daylilies.

the Rocky Mountain Laboratories in Hamilton, Montana who made a career of investigating vector-borne bacterial and viral diseases.

B. burgdorferi is a tick-borne spirochete bacterium with an average diameter of 0.2 - 0.3 microns and a length of 20-30 microns. For comparison, the human red blood cell is about eight microns, the human hair is about 100 microns, and there are 25,400 microns in an inch. Like its tick host, it is an obligate parasite (one which cannot complete its life cycle without a host). Depending on the conditions, it can assume two additional forms: a cell-wall-deficient form and a cyst form. Each form has different characteristics, advantages, and vulnerabilities. The spirochete form is very mobile and is capable of penetrating dense tissue where it can transform into one of the other forms when conditions become less positive. Within a cell, the cell-wall-deficient and cyst forms are less vulnerable to antibiotics.

Untreated, its size, structure, and motility (a corkscrew-like motion) facilitate its dissemination throughout the body where it readily impacts almost all of the major systems in the human body. Its ability to cross the blood-brain barrier accounts for the many neurological consequences, and Lyme disease acquired during pregnancy can lead to infection of the placenta and still birth.

Diagnosis

The appearance of the EM rash occurs in 80 - 90 percent of patients with Lyme disease and is sufficient to proceed with treatment without additional testing. In some patients, the rash is not evident and serologic tests are recommended.

The problem with the serological tests is that timing is critical. False positives and false negatives are common. It takes time for the body to recognize and generate antibodies to a pathogen. If the tests are performed too soon, a false negative may occur. If the tests are performed after the spirochete has disseminated and left the blood stream, a false negative may occur. A false positive can occur when antibodies from a previous infection are recognized. So, if you ever had it, you will likely always test positive even though you don't currently have an active case.

When presented with a tick, it is imperative for the medical professional to be able to classify it since the type of tick can make or break a diagnosis. The Armed Forces Pest Management Board has produced a DVD entitled "Interactive Program for Teaching Tick Morphology." It is a self-paced course of instruction that is designed to train medical personnel (or anybody for that matter) to identify ticks in the absence of a professional tick taxonomist. It is an excellent resource, and it is distributed free of charge (Fig. 4).

Another resource is the LymeMD Web page of the Lyme Disease Research Foundation (<https://www.surveymonkey.com/s/LymeMdRashQuiz>). They have developed an instructional Web page in the form of a quiz — the goal of which is to enable one to distinguish the EM rash associated with Lyme disease from other conditions like spider bites.

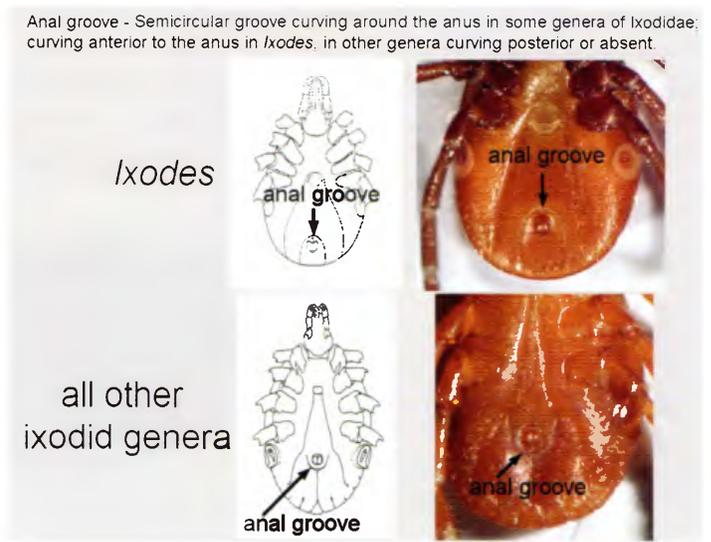


Photo DOD, Armed Forces Pest Management Board, Richard G. Robbins and George W. Schultz

▲ Figure 4: Plate from CD: "Interactive Program for Teaching Tick Morphology," explaining a definitive morphological feature that distinguishes *Ixodes* species.

Treatment

While the treatment information presented herein is believed to be current, the reader is warned that it is retrospective. Only a medical physician can diagnose and prescribe treatment for Lyme disease. In the time that it has taken for this article to be published, the treatment recommendations could have changed or be in the process of changing. Nevertheless, the information is offered with the hope of presenting as complete a picture as possible. It is not unusual for treatment protocols to change as more knowledge is obtained, and your personal physician would be a more current source for such information.

According to the National Institute of Allergy and Infectious Diseases (NIAID), a three to four weeks course of oral antibiotics cures the majority of cases. Doxycycline, a synthetic derivative of tetracycline, is the drug of choice although amoxicillin is recommended for children younger than eight years of age — and for pregnant and lactating women. For early Lyme disease or patients in Stage 1, ten days of antibiotic therapy is sufficient. Patients in Stage 2 may expect a 20 to 30 day course of antibiotic therapy. In the presence of early neurologic or cardiac manifestations, a course of ceftriaxone or cefotaxime, administered intravenously, is recommended. The literature is a bit murky when it comes to recommending treatment for phase 3 patients, there is not complete agreement in the medical community, and it underscores the rationale for not letting the disease progress to that point.

Chronic Lyme disease vs. Post-treatment Lyme Disease Syndrome vs. Late Stage Lyme Disease

In the mid 1990s, Dr. Steere became concerned that Lyme disease was becoming a handy “junkdrawer diagnosis” (his term) for everything from fibromyalgia to chronic fatigue syndrome to hypochondria. In his view, it was not appropriate for patients with no evidence of past or present Lyme disease to be treated with antibiotics which in and of themselves are not without risk. By speaking up, he created something of a fire storm and was severely criticized by the advocacy groups that had sprung up — including death threats. Advocacy groups can have a very dark side.

Chronic Lyme disease is a term used to describe three patient populations: patients with Late Stage (disseminated) Lyme disease; patients with Post-Treatment Lyme disease; and patients with Lyme-like symptoms but no evidence of Lyme disease.

The CDC estimates that ten to 20 percent of the patients treated for Lyme disease with the recommended antibiotics will later experience lingering symptoms of pain, fatigue, and muscle aches which can last for more than six months. The CDC prefers to call this “Post-Treatment Lyme Disease Syndrome (PTLDS). The cause is not known, but many medical experts believe that these late stage symptoms reflect residual damage to tissues and the patient’s immune system during the initial infection rather than a continuation of the infection. Other experts, pointing to the ability of *B. burgdorferi* to encyst and otherwise alter its gene expression, suggest that it is a continuation of the disease based on the spirochete’s ability to persist by sequestration.

Lyme Disease in Animals

Lyme disease has been reported in cows, horses, and goats. Companion animals or cats and dogs are also at risk to Lyme disease and should be monitored periodically since they are in a position to convey ticks into the family living quarters. Pets experience many of the same symptoms but lack the ability to communicate their situation — so one must be alert to subtle changes in the animal’s behavior. Symptoms include fever, joint soreness, swelling, loss of appetite, swollen glands, depression, weight loss, and fatigue. Nephritis (kidney inflammation) in dogs often results in the death of the animal. Fortunately, there are several Lyme vaccines for dogs: LYMEVAX® from Pfizer, Nobivac® Lyme from Merck Animal Health, and RECOMBITEK® Lyme by Merial. Unfortunately there is not a safe and effective vaccine for Lyme disease in cats. Merial also produces the Frontline® brand of products which provide fast-acting, long-lasting, and waterproof control of fleas and ticks in cats and dogs.

Preventing Lyme Disease

The best methods to avoid Lyme disease are: (1) limiting your personal exposure to tick infested areas; (2) walking in the center of trails when hiking; (3) wearing light colored, protective clothing and using products that contain permethrin on clothing and gear; (4) applying insect repellents containing 20% or more DEET (N,N-diethyl-m-toluamide) on exposed skin; (5) reducing tick habitat in your landscape by keeping grass short around your house and removing old log piles and leaf debris; (6) “treating” your landscape with an approved acaricide to significantly reduce the tick population; (7) discouraging deer from congregating on the property; (8) avoiding letting your dog (family pets in general) wander through

prime tick environments; and (9) after a pleasurable hour or so of gardening — performing a thorough, personal, tick check to make sure those “freckles” aren’t moving.

Tick Removal

The straight forward approach to tick removal is the best. Folk and exotic methods for removing ticks (e.g., nail polish, gasoline, petroleum jelly) can be quite counter productive. Grasping the tick as close to the skin as possible with fine tipped tweezers and gently pulling without twisting will result in the best outcome. You want to avoid crushing the tick or separating the head from the tick’s body since rough handling increases the risk of infection. After removing the tick, clean the bite area with rubbing alcohol, another disinfectant, or soap and water.

Conclusion

In the title, Lyme disease was characterized as a “clear and present danger.” The logical question then is: to whom? The short answer is that it depends on how many of the risk factors you can relate to. Do you live or work in, vacation, or recreate in areas endemic for Lyme disease? Does your vocation involve clearing brush, landscaping, forestry, farming, or wildlife and parks maintenance or management? Do you enjoy hiking, gardening, hunting, fishing, and camping? Is your region or your neighborhood overrun by deer? If you answered yes to any of these questions, then you are at risk for Lyme disease and you should exercise care.

Where are we now — some 30 years since Drs. Steere and Burgdorfer made the connection between the mysterious malady in rural Connecticut and a spirochete bacterium? Consulting the National Institutes of Health (NIH) Research Portfolio Online Reporting Tools (<http://report.nih.gov>) system, there were 84 research projects in 2011, both intramural and extramural, basic and applied, that were supported by NIH, at some of the premier biomedical research institutions in the U.S. The grants are focused on learning more about the bacterium and the disease, developing improved diagnostic methodologies, and developing a new, second generation vaccine for human Lyme disease.

From a public health point of view, more research into Lyme disease is needed. There is still much to learn, and progress will come as the investigators successfully unravel the secrets of the spirochete’s genome and develop new tools and more accurate diagnostic methodologies to ultimately improve the treatment and prognosis of Lyme disease.

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