Lyme borreliosis: Detecting the great imitator

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Lyme disease is a common inflammatory disease of North America. It is caused by the spirochetal bacterium *Borrelia burgdorferi*, which is transmitted by the bite of a small tick, *Ixodes dammini*. The disease is inconsistent in its manifestation, mimicking a wide variety of maladies, many of which are noninfectious. Currently, there is no practical means for detection of the presence of the organism, and serologic studies offer the best diagnostic aid. High titers of either immunoglobulin G (IgG) or immunoglobulin M (IgM) antibodies to *B burgdorferi* antigens indicate disease, but lower titers can be misleading. The IgM antibodies may remain after the initial infection, and IgG antibodies may remain for years. Antibiotic therapy early in the infection may interfere with antibody production, but therapy later does not appear to have a significant effect on antibody levels. Because several methods are available for the detection of antibodies and several choices for antibody detected—IgM, IgG, or combinations—the clinical laboratory should provide guidance and advice in choosing and interpreting tests.

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(Key words: Lyme disease, ticks, *Borrelia burgdorferi, Ixodes dammini, Ixodes pacificus*, infectious disease, laboratory tests, serology, antibodies)

Lyme borreliosis is a chronic, infectious, multisystem disease. This zoonotic disease was first reported by Steere and colleagues[1] in the mid-1970s as a distinct entity in the United States. The disease is named after Lyme, Conn, where the first epidemic was detected. It has since been epidemic in the Northeast, the upper Midwest, and the Far West, but its incidence has been reported in more than 40 states.

Etiology

Lyme disease is caused by a tickborne spirochetal bacterium.[2] It is the most frequently tick-transmitted disease and the most commonly reported vectorborne disease in the United States. The causative agent, *Borrelia burgdorferi*, was first identified in blood-feeding ticks by Burgdorfer and associates[3] in the early 1980s. The causative agent is transmitted to humans by the bite of the poppyseed-sized ixodid ticks, primarily *Ixodes dammini* (bear and deer ticks) and *Ixodes pacificus* (western black-legged tick). (Other ticks are *Ioxdes scapularis*, or black-legged or shoulder tick, and *Amblyomma americanum*, or lone star tick.) Quite naturally, the disease is contracted most often during warm weather when the arthropods are active. Similar diseases have been recognized in Europe since the early part of this century.[4]

The primary host for the tick larvae is the white-footed mouse, which appears to suffer no ill effects from the infection. Immature ticks acquire the organism by feeding on infected mice. The following spring, the infected nymphs transmit the disease to other animals, including dogs, horses, cows, and humans. Deer are the preferred host for adult ticks. Any verdant, outdoor areas may harbor the ticks and thus provide the potential for infection.

Clinical manifestations

As in other spirochete-caused diseases, the clinical manifestations of Lyme borreliosis often occur in stages with great variety in their clinical expression. Because the arthropod vectors are so small and their bite relatively painless, few people realize when they are bitten and the first stage of disease begins. Within 3 to 30 days after the bite, a red macule or papule appears which, over a period of days or weeks, expands to form a large annular lesion. The center of the lesion usually clears, while the outer border remains erythematous. This most charateristic feature, erythema chronicum migrans (ECM), fades over a period of weeks and is not present in or remembered by 30% to 40% of patients.

Approximately 40% of patients have multiple ECM lesions. Generally, primary lesions are asymptomatic, while secondary lesions may range from asymptomatic to pruritic and urticarial. These secondary lesions probably represent hematogenous dissemination of spirochetes, because the organism occasionally can be isolated from the blood or from the advancing border of the cutaneous lesion during this phase of the disease.

A flulike syndrome involving fever, chills, malaise, fatigue, and headache often accompanies the ECM. Less commonly reported are nausea, vomiting, and sore throat. During this phase of disease, there may be mild elevation of hepatic transaminase levels and the leukocyte count. Patients with increased levels of serum immunoglobulin M (IgM) appear to have a more complicated disease course.

Although culture or demonstration of the organism in a biopsy specimen might best afford a definitive diagnosis, such a modality is not a viable diagnostic option at present. The organisms are found in the expanding ECM lesions, blood, synovial fluid, and cerebrospinal fluid (CSF), but they are not present in sufficient amounts to satisfy diagnostic purposes. Antigenic detection and nucleic acid probes are promising but still experimental. Specific IgM antibodies begin to be detected within 2 to 3 weeks after the onset of symptoms and generally peak at about 6 weeks, then gradually decline. Therefore, patients who have ECM often have not developed detectable amounts of specific antibodies and the results of serologic tests for these antibodies will be negative.

Systemic involvement and complications

Not all untreated patients progress to the second stage of disease. As the organism spreads throughout the body, the nervous system, heart, skin, and joints are most frequently involved. Neurologic abnormalities are detected in 15% of untreated patients.[5] Most commonly seen is Bell's palsy, which is frequently associated with central nervous system infection.

Meningoencephalitis or acute meningitis occurs in 5% of patients. Oligoclonal immunoglobulin bands may be present in the CSF, indicating central nervous system involvement. Also, comparison of immunoglobulin-to-albumin ratios between the CSF and serum serves to identify patients with antibody produced in the central nervous system.

Lyme carditis develops in 8% of patients 2 to 6 weeks after early Lyme disease.[6] Myocardial conduction abnormalities resulting in various degrees of heart block are the most common cardiac manifestations. The disease may enter a chronic phase with elevations of specific IgG antibodies and a decline in the number of organisms.

Some patients enter a latent period while others have a variety of dermatologic and rheumatologic complications in addition to, or in place of, other symptoms. In other patients, these symptoms may not develop for a long time. In the United States, arthritis develops in 50% to 60% of untreated patients within days to 2 years after being bitten. Large joints, particularly the knees, are usually involved.

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- Some patients may experience transient diarrhea, which usually resolves in about a week, or abdominal discomfort. Abdominal discomfort may persist in the absence of gastric ulceration.

BRIEF SUMMARY

CONTRAINDICATIONS AND WARNINGS: Cytotec (misoprostol) is contraindicated, because of its abortifacient property, in women who are pregnant. (See *Precautions*.) Patients must be advised of the abortifacient property and warned not to give the drug to others. Cytotec should not be used in women of childbearing potential unless the patient requires nonsteroidal anti-inflammatory drug (NSAID) therapy and is at high risk of complications from gastric ulcers associated with use of the NSAID, or is at high risk of developing gastric ulceration. In such patients, Cytotec may be prescribed if the patient

- is capable of complying with effective contraceptive measures.
- has received both oral and written warnings of the hazards of misoprostol, the risk of possible contraception failure, and the danger to other women of childbearing potential should the drug be taken by mistake.
- has had a negative *serum* pregnancy test within two weeks prior to beginning therapy.
- will begin Cytotec only on the second or third day of the next normal menstrual period.

INDICATIONS AND USAGE: Cytotec (misoprostol) is indicated for the prevention of NSAID (nonsteroidal anti-inflammatory drugs, including aspirin)–induced gastric ulcers in patients at high risk of complications from gastric ulcer, eg, the elderly and patients with concomitant debilitating disease, as well as patients at high risk of developing gastric ulceration, such as patients with a history of ulcer. Cytotec has not been shown to prevent duodenal ulcers in patients taking NSAIDs. Cytotec should be taken for the duration of NSAID therapy. Cytotec has been shown to prevent gastric ulcers in controlled studies of three months' duration. It had no effect, compared to placebo, on gastrointestinal pain or discomfort associated with NSAID use.

CONTRAINDICATIONS: See boxed *CONTRAINDICATIONS AND WARNINGS*.

Cytotec should not be taken by anyone with a history of allergy to prostaglandins.

WARNINGS: See boxed *CONTRAINDICATIONS AND WARNINGS*.

PRECAUTIONS:

Information for patients: Cytotec is contraindicated in women who are pregnant, and should not be used in women of childbearing potential unless the patient requires nonsteroidal anti-inflammatory drug (NSAID) therapy and is at high risk of complications from gastric ulcers associated with the use of the NSAID, or is at high risk of developing gastric ulceration. Women of childbearing potential should be told that they must not be pregnant when Cytotec therapy is initiated, and that they must use an effective contraception method while taking Cytotec.

See boxed *CONTRAINDICATIONS AND WARNINGS*.

Patients should be advised of the following:

Cytotec is intended for administration along with nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, to decrease the chance of developing an NSAID-induced gastric ulcer.

Cytotec should be taken only according to the directions given by a physician.

If the patient has questions about or problems with Cytotec, the physician should be contacted promptly.

THE PATIENT SHOULD NOT GIVE CYTOTEC TO ANYONE ELSE. Cytotec has been prescribed for the patient's specific condition, may not be the correct treatment for another person, and may be dangerous to the other person if she were to become pregnant.

The Cytotec package the patient receives from the pharmacist will include a leaflet containing patient information. The patient should read the leaflet before taking Cytotec and each time the prescription is renewed because the leaflet may have been revised.

Keep Cytotec out of the reach of children.

SPECIAL NOTE FOR WOMEN: Cytotec must not be used by pregnant women. Cytotec may cause miscarriage. Miscarriages caused by Cytotec may be incomplete, which could lead to potentially dangerous bleeding, hospitalization, surgery, infertility, or maternal or fetal death.

Drug interactions: See *Clinical Pharmacology*. Cytotec has not been shown to interfere with the beneficial effects of aspirin on signs and symptoms of rheumatoid arthritis. Cytotec does not exert clinically significant effects on the absorption, blood levels, and antiplatelet effects of therapeutic doses of aspirin. Cytotec has no clinically significant effect on the kinetics of diclofenac or ibuprofen.

Animal toxicology: A reversible increase in the number of normal surface gastric epithelial cells occurred in the dog, rat, and mouse. No such increase has been observed in humans administered Cytotec for up to one year.

An apparent response of the female mouse to Cytotec in long-term studies at 100 to 1000 times the human dose was hyperostosis, mainly of the medulla of sternebrae. Hyperostosis did not occur in long-term studies in the dog and rat and has not been seen in humans treated with Cytotec.

Carcinogenesis, mutagenesis, impairment of fertility: There was no evidence of an effect of Cytotec on tumor occurrence or incidence in rats receiving daily doses up to 150 times the human dose for 24 months. Similarly, there was no effect of Cytotec on tumor occurrence or incidence in mice receiving daily doses up to 1000 times the human dose for 21 months. The mutagenic potential of Cytotec was tested in several *in vitro* assays, all of which were negative.

Misoprostol, when administered to breeding male and female rats at doses 6.25 times to 625 times the maximum recommended human therapeutic dose, produced dose-related pre- and post-implantation losses and a significant decrease in the number of live pups born at the highest dose. These findings suggest the possibility of a general adverse effect on fertility in males and females.

Pregnancy: Pregnancy Category X. See boxed *CONTRAINDICATIONS AND WARNINGS*.

Nonteratogenic effects: Cytotec may endanger pregnancy (may cause miscarriage) and thereby cause harm to the fetus when administered to a pregnant woman. Cytotec produces uterine contractions, uterine bleeding, and expulsion of the products of conception. Miscarriages caused by Cytotec may be incomplete. In studies in women undergoing elective termination of pregnancy during the first trimester, Cytotec caused partial or complete expulsion of the products of conception in 11% of the subjects and increased uterine bleeding in 41%. If a woman is or becomes pregnant while taking this drug, the drug should be discontinued and the patient apprised of the potential hazard to the fetus.

Teratogenic effects: Cytotec is not fetotoxic or teratogenic in rats and rabbits at doses 625 and 63 times the human dose, respectively.

Nursing mothers: See *Contraindications*. Cytotec should not be administered to nursing mothers because the potential excretion of misoprostol acid could cause significant diarrhea in nursing infants.

Pediatric use: Safety and effectiveness in children below the age of 18 years have not been established.

ADVERSE REACTIONS: The following have been reported as adverse events in subjects receiving Cytotec:

Gastrointestinal: The most frequent gastrointestinal adverse events were diarrhea and abdominal pain. The incidence of diarrhea ranged up to 40% but averaged 13% in clinical trials.

Diarrhea was dose related and usually developed early in the course of therapy (after 13 days), usually was self-limiting (often resolving after 8 days), but sometimes required discontinuation of Cytotec (2% of the patients). Rare instances of profound diarrhea leading to severe dehydration have been reported. Patients with an underlying condition such as inflammatory bowel disease, or those in whom dehydration, were it to occur, would be dangerous, should be monitored carefully if Cytotec is prescribed. The incidence of diarrhea can be minimized by administering after meals and at bedtime, and by avoiding coadministration of Cytotec with magnesium-containing antacids.

Gynecological: Women who received Cytotec during clinical trials reported the following gynecological disorders: spotting (0.7%), cramps (0.6%), hypermenorrhea (0.5%), menstrual disorder (0.3%) and dysmenorrhea (0.1%). Postmenopausal vaginal bleeding may be related to Cytotec administration. If it occurs, diagnostic workup should be undertaken to rule out gynecological pathology.

Elderly: There were no significant differences in the safety profile of Cytotec in approximately 500 ulcer patients who were 65 years of age or older compared with younger patients.

Additional adverse events which were reported are categorized as follows:

Incidence greater than 1%: In clinical trials, the following adverse reactions were reported by more than 1% of the subjects receiving Cytotec and may be causally related to the drug: nausea (3.2%), flatulence (2.9%), headache (2.4%), dyspepsia (2.0%), vomiting (1.3%), and constipation (1.1%). However, there were no significant differences between the incidences of these events for Cytotec and placebo.

Causal relationship unknown: The following adverse events were infrequently reported. Causal relationships between Cytotec and these events have not been established but cannot be excluded: aches/pains, asthenia, fatigue, fever, rigors, weight changes, rash, dermatitis, alopecia, pallor, breast pain, abnormal taste, abnormal vision, conjunctivitis, deafness, tinnitus, earache, upper respiratory tract infection, bronchitis, bronchospasm, dyspnea, pneumonia, epistaxis, chest pain, edema, diaphoresis, hypotension, hypertension, arrhythmia, phlebitis, increased cardiac enzymes, syncope, GI bleeding, GI inflammation/infection, rectal disorder, abnormal hepatobiliary function, gingivitis, reflux, dysphagia, amylase increase, anaphylaxis, glycosuria, gout, increased nitrogen, increased alkaline phosphatase, polyuria, dysuria, hematuria, urinary tract infection, anxiety, change in appetite, depression, drowsiness, dizziness, thirst, impotence, loss of libido, sweating increase, neuropathy, neurosis, arthralgia, myalgia, muscle cramps, stiffness, back pain, anemia, abnormal differential, thrombocytopenia, purpura, ESR increased.

Important note: Complete prescribing information should be consulted prior to use.

DOSAGE AND ADMINISTRATION: The recommended adult oral dose of Cytotec for the prevention of NSAID-induced gastric ulcers is 200 mcg four times daily with food. If this dose cannot be tolerated, a dose of 100 mcg can be used. Cytotec should be taken for the duration of NSAID therapy as prescribed by the physician. Cytotec should be taken with a meal, and the last dose of the day should be at bedtime.

Renal impairment: Adjustment of the dosing schedule in renally impaired patients is not routinely needed, but dosage can be reduced if the 200-mcg dose is not tolerated.

1/31/91 • P91CY5660V

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Diagnosis

Because the symptoms during the various phases of Lyme borreliosis often result in a complex differential clinical diagnosis, serologic testing has become the most common laboratory method for diagnosing Lyme disease.[7] Immunoglobulin G antibodies generally can be detected at about 6 weeks after the appearance of ECM and may persist for years. Although IgM antibodies usually decline, they may also remain elevated in certain instances that as yet remain unclear. Therefore, an elevated IgM response, contrary to the usual understanding, may not indicate acute infection.

Unfortunately, the serologic picture may be complicated by many factors. One is that early antibiotic therapy interferes with the development of specific antibodies. Also, because there is cross-reactivity with other spirochetes such as treponema and because several species of treponema inhabit the body as normal flora, low levels of antibody are present in the general population.[8] Furthermore, patients with serology tests positive for antibodies to *Treponema pallidum* will also have high titers of cross-reacting antibody to *Borrelia*. As in syphilis, the presence of significant titers of IgG antibody to the organism does not distinguish between active infection and past disease. Fortunately, patients with Lyme disease do not develop antibodies to rapid plasma reagin (RPR) or Venereal Disease Research Laboratory (VDRL) antigens found in syphilis. Therefore, the RPR and VDRL tests can be used to aid in distinguishing between Lyme disease and syphilis.

As a great disease imitator, Lyme borreliosis must be distinguished from certain autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus. Quite naturally, patients with these types of diseases often have false-positive reactions to serologic tests for *B burgdorferi*. These reactions perhaps are due to immune complexes to *Borrelia* antigens and nonspecific rheumatoid factor activity. As patients progress to chronic, untreated Lyme borreliosis, specific antibody titers increase dramatically, thus making it easier for serologic diagnosis at this stage of disease.

Because Lyme borreliosis is similar to other diseases and 80% of untreated patients go on to second- and third-stage complications, the serologic testing of patients has expanded dramatically over the past few years. There are now at least ten manufacturers of commercial kits for the detection of antibodies to *B burgdorferi*. Two major types of tests are performed to detect antibodies to *Borrelia*: The indirect fluorescent antibody test (IFA) uses the whole organism as the antigen, and the enzyme-linked immunosorbent assay (ELISA) may use the entire organism or certain antigenic components of the organism.[9] Kits may detect only IgG antibodies, only IgM antibodies, or all classes of antibody.

The lack of standardization regarding what constitutes a positive reaction, the lack of experience in interpretation among technicians in smaller laboratories, and the lack of adequate proficiency testing contribute to some degree of confusion, especially in testing patients with possible early Lyme disease. It does not appear that the antibodies to *Borrelia* are protective, nor does there appear to be a test of cure, because the IgG antibodies remain for years.

Currently, the importance of a thorough history and physical examination to the diagnosis of early Lyme borreliosis cannot be overemphasized.[10] Erythema chronicum migrans, the possibility of a tick bite, and a flulike illness remain the most consistent diagnostic criteria for early disease. Serologic testing for specific antibody, even of the IgM class, at this stage may be negative and may remain negative if antibiotic therapy is initiated. Serologic tests positive for specific antibody to *B burgdorferi* are much more likely during untreated second- and third-stage disease; however, a history is much more clouded at this stage and symptoms lend themselves to a broad spectrum of diseases.

Summary

There is no accepted treatment regimen for Lyme borreliosis and no apparent criteria for determining the success of treatment. Approximately 50% of patients with early disease who apparently respond to antibiotic therapy con-

tinue to have intermittent symptoms for years. The possibility of reinfection, other similar but separate diseases, or exacerbation of Lyme disease all remain in the clinical picture. Serologic testing should be used only in conjunction with clinical diagnosis and interpreted in the context of the illness. The clinical laboratory should readily provide aid in the interpretation of serologic tests.

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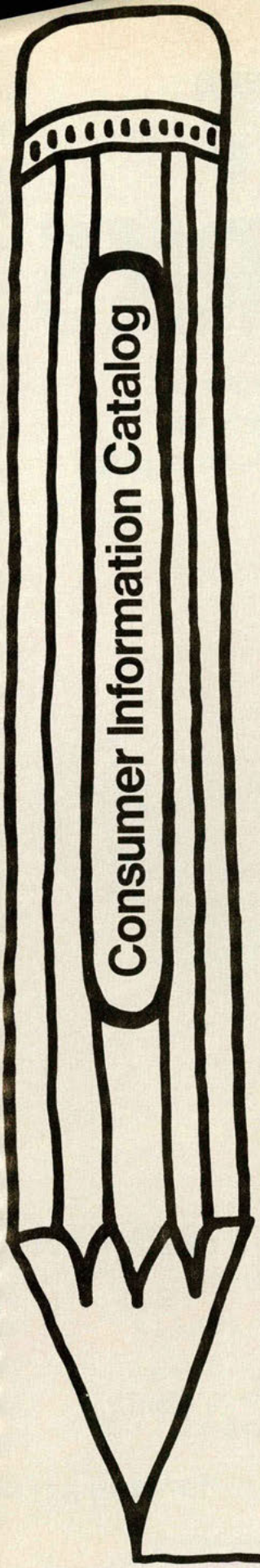

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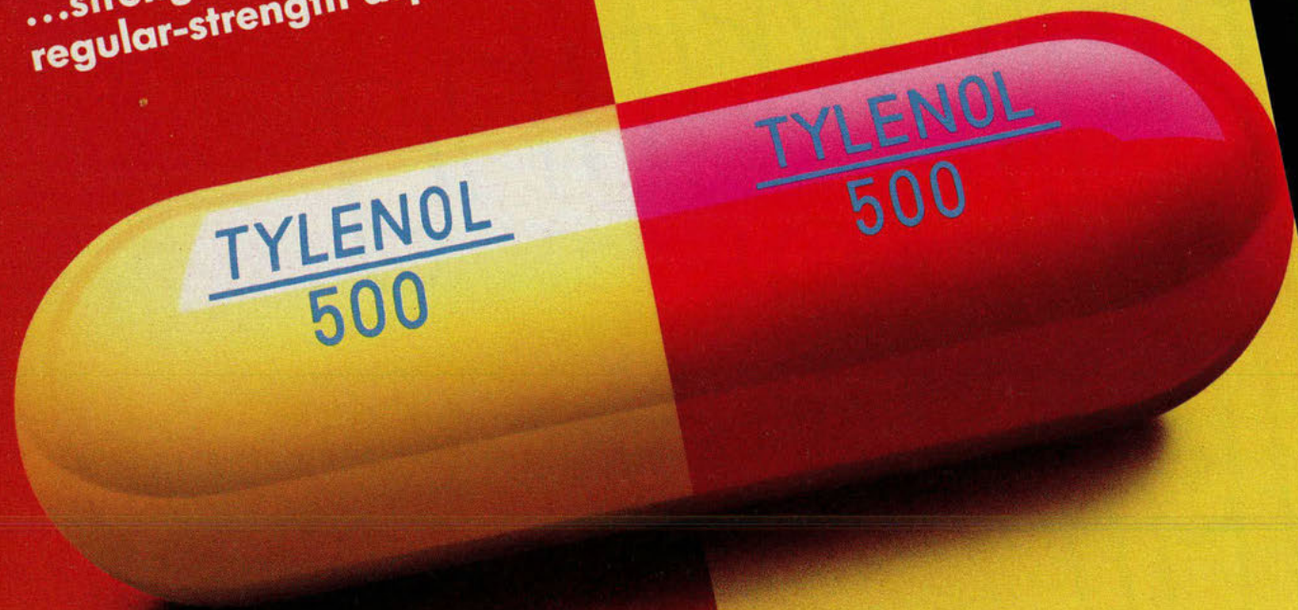

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