

Spring 5-12-2018

# A Pharmacist's Guide to the Treatment of Lyme Disease

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## Recommended Citation

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# **A Pharmacist's Guide to the Treatment of Lyme Disease**

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## **Abstract**

Lyme disease is a tick-borne illness with significant impact on the United States healthcare system. An estimated 329,000 cases of Lyme disease occur annually in the United States, making it one of the top ten most common Nationally Notifiable diseases to the Centers for Disease Control and Prevention (CDC) National Notifiable Diseases Surveillance System (NNDSS). The treatment of Lyme disease is responsible for approximate direct medical costs between \$712 million to \$1.3 billion annually. This comprehensive guide is intended to be used by healthcare professionals, particularly pharmacists, to assist in the evidence-based treatment and management of Lyme disease.

Keywords: Lyme disease, *Ixodes scapularis*, tick, *Borrelia burgdorferi*, borreliosis, antibiotic, pharmacy

## **Introduction**

Doctor of Pharmacy candidates are tasked to complete a seminar presentation during their fourth year, which is used to educate the cohort and prepare them to treat the chosen disease state during their individual practice. This comprehensive guide was created to assist future pharmacists in their clinical management of Lyme disease.

The learning objectives targeted with this project were to assist the reader to identify causative agents and vectors of Lyme disease; recognize the typical presenting signs and symptoms; recommend an appropriate antimicrobial therapy for a patient with Lyme disease; and effectively counsel patients on preventive measures they can take to protect themselves from developing Lyme disease.

## **A Brief History of Lyme Disease**

More than a hundred and thirty years ago, a chronic skin rash was described which came to be known as erythema migrans. In the early 1970's, children and adults in Lyme, Connecticut began complaining of symptoms including: swollen knees, paralysis, rashes, headaches, and severe chronic fatigue. The children who developed this mystery disease all said that they developed the rash and then arthritis, and they recalled being bitten by a tick. In 1981, Dr. Burgdorferi was a scientist studying Rocky Mountain Spotted Fever, which is another tick-

borne illness. He found the connection between deer ticks and the disease afflicting the people of Lyme. He also discovered a type of bacteria called a spirochete, which was carried by the ticks that were responsible for causing the disease. In 1982, the spirochete was named *Borrelia burgdorferi* in honor of Dr. Burgdorfer's discovery. In present times Lyme disease is now one of the top ten notifiable diseases by the Centers for Disease Control and Prevention (CDC), and one of the fastest-growing vector-borne infections in the United States. The CDC has estimated that there are over 329,000 new cases of Lyme each year. This disease that started as an East Coast phenomenon has now been reported in all states except for Hawaii.

### ***Ixodes scapularis***

The tick responsible for carrying Lyme disease is *Ixodes scapularis*, also known as a blacklegged tick or the deer tick. A typical lifecycle for *I. scapularis* lasts two years, and during this time the ticks go through four life stages: in the spring months it starts off life as an egg, which develops into a larva during the summer months, to a nymph in the next spring, and finally to an adult in the fall, during which time eggs are laid and the cycle begins anew. After the eggs hatch, ticks must have a blood meal at each stage to survive and progress to the next life stage. The spring and summer months of the nymph stage are when the risk of human infection is the greatest. Ticks cannot fly or jump to find their host - instead they hold onto the tip of a blade of grass or leaves with their lower legs,

and extend their upper legs outward in a position known as “questing”. This is how they wait for prey to pass by for them to grab and attach themselves to. When the tick finds a site to feed from, it will grasp the skin and cut into the surface. The tick then inserts its tiny feeding tube and secretes a cement substance that helps keep them attached during the meal. The feeding tube may also have barbs that help keep them secured in place. In the tick’s saliva is an anesthetic, so when bitten the prey cannot actually feel the tick attached. If the tick has chosen a spot where it is not able to be seen, it can go unnoticed for days. During this time the tick feeds on the blood of its victim, and becomes engorged. *I. scapularis* is very small, initially approximately the size of a poppy seed, but grows considerably during the blood meal and the longer they are attached.

### ***Borrelia burgdorferi***

The infectious spirochete transmitted in the saliva of *I. scapularis* during feeding and the causative agent of Lyme disease itself is *Borrelia burgdorferi*. It exhibits the standard corkscrew shape. Another common spirochete responsible for disease in humans is *Treponema pallidum*, the causative agent of syphilis.

### **Epidemiology**

Nearly all cases of Lyme disease are reported in the northeastern region of the United States. In 2013, 95% of cases were reported from just fourteen states:

Connecticut, Delaware, Maine, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont, Virginia, and Wisconsin. It is important to note that each case recorded was based upon the person's residence, not necessarily where they were infected. In 2015 there were no cases reported from Hawaii, and only one travel-related case from Alaska. As climate change causes warmer temperatures and alters weather patterns, it is predicted that tick habitats will shift further into the central United States and northward into Canada.

## **Diagnosis**

The CDC recommends using the two-tiered testing decision tree to diagnose Lyme disease. The first step is an enzyme immunoassay (EIA) or an immunofluorescence assay (IFA). If either test results as negative, it is likely not Lyme disease, and consideration should be given to an alternative diagnosis. However if the first test result is positive, one can differentiate based on the length of symptoms which second test is appropriate. If a patient has had symptoms for less than or equal to 30 days, then an IgM or IgG Western blot should be performed to confirm the diagnosis of Lyme disease. If a patient has had symptoms for greater than 30 days, then an IgG Western blot is the only appropriate second test.

## **Associated Conditions**

Other tick-borne diseases transmitted by *I. scapularis* include human granulocytic anaplasmosis and babesiosis. It is rare for co-infection with Lyme disease at the same time from a single tick bite, but it is possible. Other tick-borne diseases include: Southern Tick-Associated Rash Illness (STARI), Rocky Mountain Spotted Fever, tularemia, Colorado tick fever, Tickborne relapsing fever (TBRF), and Powassan disease. Signs and symptoms of STARI resemble those of Lyme disease, and patients with suspected STARI often receive the same antibiotics recommended in the treatment of Lyme disease.

## **Signs and Symptoms**

Typically when patients present with Lyme disease they will have at least one of the following cardinal symptoms: erythema migrans rash, Bell's Palsy, and/or lymphadenopathy. The immediate period after infection with *B. burgdorferi* is called the localized stage. Commonly this is when patients experience the erythema migrans rash, which is a red ring-like or Bull's-eye type rash that expands from the site of the bite. However, it is important to know that this classic rash is not present in all cases. Patient may also complain of non-specific flu-like symptoms – malaise, headaches, fevers, myalgias, arthralgias – and/or lymphadenopathy. If the disease is not treated at this point and the infection is allowed to spread throughout the body, this is called the disseminated stage. Patients can develop multiple secondary annular rashes, continue experiencing

flu-like symptoms, and/or lymphadenopathy. Disseminated disease can also manifest differently depending on what body site it has spread to.

Rheumatologic manifestations may include: transient, migratory arthritis and effusion in one or more joints; migratory pain in tendons, bursae, muscles, and bones; and/or Baker's cysts. Cardiac manifestations may include: conduction abnormalities, including atrioventricular node block, called Lyme carditis; myocarditis, and/or pericarditis. Neurological manifestations may include: Bell's Palsy or other cranial neuropathies; meningitis; motor and sensory radiculoneuropathy, mononeuritis multiplex; subtle cognitive difficulties; and although rare, may progress to: encephalitis, encephalomyelitis, subtle encephalopathy, and/or pseudotumor cerebri. The infection and can also spread to the eyes, presenting as conjunctivitis, keratitis, or uveitis; or to the liver, manifesting as mild hepatitis; or to the spleen as splenomegaly.

### Erythema Migrans

The erythema migrans rash is typically what most people associate with Lyme disease. Unfortunately, the Bull's-eye rash may not always be present or may take an alternative form. Lesions may appear solid, or be a bluish-purple hue, or perhaps be crusted or blistering. The rash is not painful or pruritic, but may be warm to the touch. If the early, localized infection is not treated, it may disseminate and present as multiple secondary circular rashes. It is important for pharmacists to be able to recognize the erythema migrans rash and its many

presentations for purposes of triaging and referring patients to appropriate care. With this responsibility comes a need to differentiate and recognize rashes that are not erythema migrans. These include:

- Insect bite hypersensitivity, which is a large itchy rash caused by an allergic reaction to an insect bite – this includes allergic reactions to tick bites, which typically appear within the first 48 hours of attachment, and are generally less than 5 centimeters in diameter around the site of the bite
- Fixed drug reactions, which are a skin condition that occurs up to two weeks after taking a medication, and reappears at the same site every time that particular medication is taken
- Ringworm (*Tinea corporis*), which is a common fungal skin infection that causes circular “ring” shaped rashes that are usually red and itchy with raised edges
- Pityriasis rosea rash, which is a rash of unknown cause that can appear round or oval, pink, and scaly with a raised border. It can sometimes be itchy, and commonly occurs in large patches
- Granuloma annulare rash, which presents as reddish bumps arranged in a circle or ring
- Urticaria multiforme (also known as hives), which is often caused by an allergic reaction to food, infection, or medication, and may burn or itch

Erythema migrans rash is still the most common clinical manifestation of Lyme disease, with 70% of cases reported between 2001 to 2016 documented as erythema migrans. Other manifestations are less common, and patients may present with multiple symptoms.

### **Laboratory Values**

In general, laboratory findings may include elevated erythrocyte sedimentation rate, mildly elevated hepatic transaminases, and/or microscopic hematuria or proteinuria. In cases of Lyme meningitis, cerebrospinal fluid (CSF) typically shows lymphocytic pleocytosis, slightly elevated protein, and normal glucose levels.

### **Natural History**

Most patients receive treatment for the Lyme disease early after presentation with the erythema migrans rash. There is one documented case of a 71-year old woman who presented to her rheumatologist after what she believed was approximately a two-year history of Lyme disease. In her case she attempted to utilize homeopathic remedies for her symptoms, which progressed from the erythema migrans rash all the way to Lyme arthritis, which left her bedridden for a number of days before she accepted antimicrobial treatment she had refused previously. Eventually she was treated with doxycycline for 30 days and her symptoms resolved.

## **Goals of Therapy**

The goals in treating Lyme disease are: to eliminate the *Borrelia burgdorferi* infection, to resolve symptoms and return patients to their prior quality of life, and to prevent patients from experiencing recurrent episodes from an untreated or inadequately treated infection. The biggest impact pharmacists can make is by helping to prevent patients from developing Lyme disease in the first place, and preventing them from becoming re-infected at a later date.

## **Prevention**

Some advice pharmacists can offer to patients to prevent Lyme disease includes:

- Wear hats and tuck in their hair
- Wear light-colored clothes
- Cover wrists and ankles, tuck pants in to socks and wear long-sleeves
- Using at least 20% DEET, picardin, or IR3535 repellent on exposed skin
- Use at least 0.5% permethrin products to treat clothing and gear (boots, pants, socks, tents)
- Treat pets for ticks as recommended by a veterinarian
- Check for ticks daily, especially in areas ticks may be able to attach or hide, such as: under arms, in and around ears, inside belly buttons, behind knees, around the waist, hairline, and scalp

- Shower soon after being outdoors
- Launder clothes in hot water and/or tumble them in a hot dryer for one hour

## **Tick Removal**

Should someone be bitten by a tick, the key is to remove the tick as soon as possible, with goals of preventing the spread of *Borrelia* infection and progression to Lyme disease. There are a lot of “home remedies” about using nail polish, petroleum jelly, or heat (such as from a lighter or match) to try and encourage the tick to detach – these methods are not recommended and are not efficacious. The recommended method of tick removal is to use pointy tweezers to grasp the tick as close to the skin as possible. It is important to grasp the tick without squishing the body, which would encourage the tick to expel the *Borrelia*. Pull upward with steady, even pressure – do not twist or jerk the tick, which can cause the mouthparts to break off and remain in the skin. If this happens, and the patient is unable to remove them with a pair of tweezers, leave them alone and allow the skin to heal. After successfully removing the tick, be sure to thoroughly clean the bite area and hands with rubbing alcohol, iodine scrub, or soap and water.

## Antimicrobial Prophylaxis

Generally speaking, use of antimicrobial prophylaxis is NOT recommended for prevention of Lyme disease after a recognized tick bite. The only patients eligible for antimicrobial prophylaxis are those who meet all of the same criteria of the study it is based upon:

- The attached tick must be reliably identified as an adult or nymphal stage *I. scapularis*, estimated to have been attached for at least 36 hours based upon the degree of blood engorgement or certainty about the time of exposure to the tick
- Must be able to start prophylaxis within 72 hours of the tick being removed
- Local rates of *B. burgdorferi* infection in *I. scapularis* must be at least 20% - typically in parts of New England, the mid-Atlantic states, Minnesota, and Wisconsin
- Must be eligible to receive doxycycline, which is contraindicated in pregnant women and children less than 8 years old, and those with a documented allergy

For patients that meet all of these criteria, the only recommended agent is a single dose of 200 mg doxycycline in adults, or 4 mg/kg (maximum dose 200 mg) in children age 8 years or older.

## **Non-Pharmacologic Therapy**

There are numerous natural products that make claims for potential use in Lyme disease, but they offer no evidence or data about their effectiveness in Lyme disease. These agents include: acetyl-L-carnitine, alpha-lipoic acid, beta-glucans, bifidobacteria, calcium, coenzyme Q10, fish oil, ginkgo leaf, lactobacillus, L-carnitine, magnesium, molybdenum, saccharomyces boulardii, vitamin B<sub>6</sub>, vitamin B<sub>12</sub>, and vitamin C. I would not recommend any of these products to patients, as there is nothing known about their use in Lyme disease.

## **Pharmacologic Therapy**

Most patients are eligible for oral antimicrobial therapy, with choice of agent and appropriate duration based on their age, medication allergies, and the severity and manifestations of their infection. Severe cardiac or neurological manifestations justify use of intravenous antimicrobials, and typically longer durations of therapy.

### Doxycycline

Indications:

- Lyme disease (*Borrelia* spp. Infection) (off-label)

Dosage - Adults: PO:

- *Prophylaxis: 200 mg single dose*
  - **\*\*NOTE: only in patients who meet ALL criteria\*\***
- *Treatment, early localized (eg, erythema migrans): 100 mg BID x 14 days (10-21 days)*
- *Treatment, arthritis without neurologic involvement (early or late disease): 100 mg BID x 28 days*
- *Treatment, early disseminated, mild neurologic involvement (isolated facial nerve palsy): 100 mg BID x 14-28 days*
  - **\*\*NOTE: NOT recommended for serious neurologic disease\*\***

Dosage – Children ≥8 years:

- *Prophylaxis: 4 mg/kg (max 200 mg) single dose*
  - **\*\*NOTE: initiate within 72 hours of tick removal\*\***
- *Treatment (early Lyme disease without neurologic manifestations): 1-2 mg/kg BID x 10-21 days (max 100 mg/dose)*
- *Treatment (meningitis and other early neurologic manifestations): 4-8 mg/kg/day in 2 divided doses x 10-28 days (max 200 mg/dose)*

Monitoring Parameters:

- CBC, renal and liver function tests periodically with prolonged therapy

Adverse Effects:

- Common – photosensitivity; diarrhea; nasopharyngitis

- Serious – drug reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis; *Clostridium difficile* diarrhea; hepatotoxicity; hypersensitivity reaction; pseudotumor cerebri

## Amoxicillin

### Indications:

- Lyme disease (excluding neurologic disease) (off-label use)
- Lyme neuroborreliosis (off-label use) (when doxycycline is contraindicated)

### Dosage – Adults: PO:

- *Acrodermatitis chronica atrophicans*: 500 mg TID x 21 days
- *Erythema migrans*: 500 mg TID x 14-21 days
- *Lyme arthritis*: 500 mg TID x 28 days
- *Lyme carditis (mild)*: 500 mg TID x 14-21 days
- Lyme neuroborreliosis (when doxycycline is contraindicated): PO 500 mg TID x 14-21 days
  - \*\*NOTE: PO regimens should be reserved for patients with cranial nerve palsy without evidence of meningitis\*\*

### Dosage – Children:

- PO 50 mg/kg/day divided Q8H (max 500 mg/dose)

#### Dose Adjustments:

- GFR 10-30 mL/min: 250-500 mg Q12H
- GFR <10 mL/min: 250-500 mg Q24H

#### Monitoring Parameters:

- If prolonged therapy: renal, hepatic, and hematologic function periodically
- At beginning and throughout therapy – infection
- Signs of anaphylaxis during first dose

#### Adverse Effects:

- Common – rash; diarrhea, nausea, vomiting; mycotic vulvovaginitis
- Serious – erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis; *Clostridium difficile* diarrhea; anaphylaxis, hypersensitivity reaction

#### Drug Interactions:

- Warfarin (increased risk of bleeding)

#### Cefuroxime axetil

Indications:

- Treatment of adults and adolescents  $\geq 13$  years with Lyme disease (early)

Dosage – Adults:

- PO 500 mg BID x 20 days

Dosage – Children:

- PO 500 mg BID x 20 days

Dose Adjustments:

- CrCl 10-20 mL/min: 750 mg Q12H
- CrCl  $< 10$  mL/min: 750 mg Q24H

Monitoring Parameters:

- Renal, hepatic, and hematologic function periodically with prolonged therapy
- Signs and symptoms of anaphylaxis during first dose

Adverse Effects:

- Common – eosinophil count raised

- Serious – erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis; thrombocytopenia; anaphylaxis, hypersensitivity reaction; interstitial nephritis

## Erythromycin

### Indications:

- (alternative to first-line) - Early localized or early disseminated Lyme disease associated with erythema migrans, or borreliosis lymphocytoma

### Dosage – Adults:

- 500 mg PO QID x 14-21 days

### Dosage – Children:

- 12.5 mg/kg PO QID x 14-21 days (max 2000 mg/day)

### Monitoring Parameters:

- Symptomatic improvement
- If concomitant lovastatin: creatine kinase and transaminase serum concentrations

### Adverse Effects:

- Common – diarrhea, loss of appetite, nausea, stomach cramps, vomiting

- Serious – prolonged QT interval, Torsades de pointes, ventricular arrhythmia; Stevens-Johnson syndrome, toxic epidermal necrolysis; *Clostridium difficile* colitis, pancreatitis; cholestatic hepatitis, hepatitis; anaphylaxis; seizure; ototoxicity; interstitial nephritis

#### Drug Interactions: LOTS!

- Contraindicated:
  - Simvastatin, Lovastatin – increased risk of myopathy or rhabdomyolysis
  - Ergot derivatives – increased risk of acute ergotism (nausea, vomiting, vasospastic ischemia)
  - Cisapride, Fluconazole – cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
  - Colchicine – colchicine toxicity
  - Ziprasidone, Saquinavir, Posaconazole – QT-interval prolongation
- Major:
  - Digoxin – digoxin toxicity (nausea, vomiting, arrhythmias)
  - Warfarin – increased risk of bleeding
  - Fentanyl – increased risk of fentanyl toxicity

#### Ceftriaxone

#### Indications:

- Lyme disease (off-label use)

#### Dosage – Adults:

- **IV** 2 g once daily x 14 days (neurologic), or x 21-28 days (carditis), or x 28 days (arthritis with neurologic manifestations)
- **\*\*NOTE: SAFE in pregnancy\*\***

#### Dosage – Children: IM, IV:

- *Atrioventricular heart block or carditis:* 50-75 mg/kg once daily (max 2,000 mg) x 14-21 days
- *Encephalitis or other late neurologic disease:* 50-75 mg/kg once daily (max 2,000 mg) x 14-28 days
- *Neurologic:* 50-75 mg/kg once daily (max 2,000 mg) x 14 days
- *Meningitis:* 50-75 mg/kg once daily (max 2,000 mg) x 14-21 days
- *Recurrent arthritis:* 50-75 mg/kg once daily (max 2,000 mg) x 14-28 days

#### Monitoring Parameters:

- Prothrombin time/INR
- Signs and symptoms of anaphylaxis

#### Adverse Effects:

- Common – warmth, tightness, or induration at injection site; diarrhea; eosinophil count raised, thrombocytosis

- Serious – erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis; *Clostridium difficile* colitis; hemolytic anemia; hypersensitivity reaction; kernicterus of newborn; renal failure; injury of lung

#### Drug Interactions:

- Contraindicated:
  - Ringer's solution, Calcium acetate, Lactated Ringer's solution – formation of ceftriaxone-calcium precipitates, contraindicated in neonates
- Warfarin – increased risk of bleeding
- Cyclosporine – cyclosporine toxicity (renal dysfunction, cholestasis, paresthesias)

#### Cefotaxime

#### Indications:

- Lyme disease (as an alternative to ceftriaxone)

#### Dosage – Adults:

- *Cardiac manifestations*: **IV** 2 g Q8H x 14-21 days
- *CNS manifestations*: **IV** 2 g Q8H x 10-28 days

#### Dosage – Children:

- *Cardiac or CNS manifestations*: IV 150-200 mg/kg/day in divided doses  
Q6-8H x 14-28 days (max 6 g daily)

#### Dose Adjustments:

- CrCl <20 mL/min/1.73 m<sup>2</sup>: reduce dose by 50%

#### Monitoring Parameters:

- Signs and symptoms of anaphylaxis during first dose
- CBC with differential (especially with long courses >10 days)
- Renal function

#### Adverse Effects:

- Common – injection site pain, injection site phlebitis, rash; diarrhea, vomiting
- Serious – cardiac dysrhythmia; erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis; agranulocytosis, granulocytopenic disorder, leukopenia, neutropenic disorder, pancytopenia; hypersensitivity reaction

#### Drug Interactions:

- Warfarin – increased risk of bleeding

- Probenecid – increased cefotaxime plasma concentrations

## Penicillin G

### Indications:

- Lyme disease

### Dosage – Adults:

- Early Lyme disease, acute neurological disease manifested by meningitis or radiculopathy, or seventh-cranial-nerve palsy with CNS involvement: 18-24 million units/day **IV** divided Q4H x 14 days (10-28 days)
- Initial treatment of hospitalized patients with Lyme carditis: x 14-21 days
- Lyme arthritis with neurological involvement, including those refractory to oral therapy, or late neurologic Lyme disease: 14-28 days

### Dosage – Children:

- Early Lyme disease, acute neurological disease manifested by meningitis or radiculopathy, or seventh-cranial-nerve palsy with CNS involvement: 200,000-400,000 units/kg/day IV divided Q4H x 14 days (10-28 days) (max 18-24 million units daily)
- Initial treatment of hospitalized patients with Lyme carditis: x 14-21 days
- Lyme arthritis with neurological involvement, including those refractory to oral therapy, or late neurologic Lyme disease: 14-28 days

### Dose Adjustments:

- CrCl <10 mL/min/1.73 m<sup>2</sup>, IV/IM: administer full loading dose, followed by one-half loading dose Q8-10H
- CrCl >10 mL/min/1.73 m<sup>2</sup> and uremia, IV/IM: administer a full loading dose, followed by one-half loading dose Q4-5H

### Monitoring Parameters:

- Signs and symptoms of anaphylaxis with first dose

### Adverse Effects:

- Serious – congestive heart failure; electrolyte imbalance; anaphylaxis, hypersensitivity reaction; coma, seizure

### Drug Interactions:

- Methotrexate – methotrexate toxicity
- Warfarin – increased risk of bleeding
- Bupropion, Donepezil – lower seizure threshold

### Special Populations

#### Pregnancy

- PO amoxicillin 500 mg three times daily for 2-3 weeks

- If allergy: cefuroxime axetil 500 mg twice per day
- There are no reports of Lyme disease transmission from breast milk

## Children

- Less than 8 years old:
  - PO amoxicillin three times daily for 2-4 weeks
    - If allergy: cefuroxime axetil twice daily
- Over 8 years old:
  - Doxycycline twice daily for 2-4 weeks
    - If allergy: amoxicillin or cefuroxime axetil

## Monitoring

During therapy it is important to monitor patients for resolution of their symptoms, and for signs and symptoms of unresolved disease or other tick-borne diseases (such as new or persistent skin lesions or symptoms of viral-like illness). If patients do not receive an adequate course of antibiotics they may also experience subsequent episodes of Lyme disease.

## **Trial #1: Topical Azithromycin for the Prevention of Lyme Borreliosis: a Randomised, Placebo-Controlled, Phase 3 Efficacy Trial**

### Study Objectives / Purpose

The objective of this study was to determine if use of topical azithromycin in adults bitten by European ticks would reduce the number who developed Lyme borreliosis when compared with placebo, and to assess the safety and tolerability of the topical gel product.

### Brief Background

The Infectious Diseases Society of America (IDSA) and the European Union Concerted Action on Lyme Borreliosis (EUCALB) recommend oral doxycycline treatment for patients after they have developed erythema migrans. Studies performed in mice showed that topical doxycycline had no activity against *B. burgdorferi*, but a single application of topical azithromycin within 72 hours of infection inhibited the growth and survival of the bacteria.

### Funding

The study was funded by Ixodes AG, a Swiss pharmaceutical company responsible for manufacturing the product, Ixogel®.

### Study Design and Methodology

This was a randomized, double-blind, placebo-controlled, multicenter, phase 3 efficacy trial performed in Germany and Austria.

### Patient Selection and Enrollment

The study included adults age 18 to 79 years of age who presented within 72 hours after a recognized tick bite, and either had the tick still attached or had collected it. Patients were excluded if they had documented Lyme borreliosis in the previous 12 months, if they had positive serology for *B. burgdorferi* sensu lato within the previous 2 years, or if they had a history of a tick bite in the previous 60 days.

### Interventions

Participants were randomized to receive either a topical 10% azithromycin (20 mg azithromycin per gel drop) or an identical colorless ethanol-based gel placebo. Both groups were instructed to use their assigned gel twice a day for 3 days

### Outcome Measures / Endpoints

The primary outcome was treatment failure at 8 weeks, which was defined as erythema migrans and/or seroconversion in participants that had been seronegative at baseline, had no further tick bites during the study, and had serology results available for evaluation at 8 weeks. Researchers also performed a post-hoc analysis using only the erythema migrans rash. Secondary outcomes included treatment failure at 8 weeks in the safety population, modified intention-to-treat (mITT) population, and per-protocol populations; and reduction in number of participants with seroconversion in all populations. They

also evaluated safety endpoints of local skin tolerability and overall safety of the topical 10% azithromycin gel.

### Statistical Analyses

Statistics appropriately evaluated included: intention-to-treat (ITT), odds ratios, absolute risk reduction, and number needed to treat.

### Enrollment and Baseline Characteristics

685 participants were randomized to the azithromycin group, and 686 participants were randomized to the placebo group. 174 participants were included in the reanalyzed ITT population. Participants were almost exclusively white, and the majority were from Germany – this is not surprising considering the study was conducted in Europe. Only 17% of participants were found to have been bitten by an infected tick.

### Summary of Primary and Secondary Outcomes

- 22 treatment failure events occurred in the ITT population by the first interim analysis ( $p = 0.47$ )
- At 8 weeks, numbers were similar in the safety population ( $p = 0.17$ ), the mITT population ( $p = 0.34$ ), and the per-protocol population ( $p = 0.30$ )

- In the per-protocol population, the number of participants with erythema migrans was lower in the azithromycin group than in the placebo group at day 30 (0 vs. 5)
- At day 30, the number of patients in the reanalyzed ITT with erythema migrans was 0 in the azithromycin group vs. 7 in the placebo group; absolute risk reduction = 8.05%
- More than 99% of participants had either no skin reactions, or doubtful or mild skin tolerance events

#### Brief Summary of Authors' Main Discussion Points

- The trial was stopped early because futility analysis showed the pre-specified efficacy endpoint (reduction in number of participants with erythema migrans, seroconversion, or both) compared with placebo at 8 weeks was not reached in the ITT population
- Tolerability and safety outcomes did not differ between groups
- *Exploratory* post-hoc analysis of only erythema migrans in only participants bitten by infected ticks suggested azithromycin was superior to placebo

#### Authors' Conclusions

The authors concluded that although the results of this analysis suggested some preventative efficacy with topical azithromycin, it was not sufficiently powered to prove superiority over placebo in preventing Lyme borreliosis. Therefore, the

data were deemed to be exploratory and need to be confirmed in sufficiently powered future studies with restricted clinical primary outcome measures.

### Study Strengths

Patients were given precise application instructions, which were also demonstrated by a physician. The researchers also chose an appropriate agent with potential to be used in nearly all patients.

### Study Limitations

Unfortunately, Lyme disease in the United States is caused by *B. burgdorferi*, which is a different, faster disseminating *Borrelia* than the European *Borrelia afzelii*. The sample size was too small and therefore the study was underpowered. Additionally, there were inconsistent criteria used for the diagnosis of erythema migrans rash, which can have varying presentations.

### Applicability and Impact on Pharmacists / Healthcare Providers

Patients may ask pharmacists about topical options for erythema migrans rashes and tick bites, especially over-the-counter products. Patients may also be reluctant to complete a two-week course of oral antibiotics.

### Conclusions and Recommendations

Future studies could provide better insight into potential topical pharmacological prophylactic agents. These agents could be used to address the diagnostic gap for patients with atypical or absent erythema migrans rash or unnoticed tick bites. They may also offer an alternative to oral antibiotics, and utilize a shorter treatment courses to increase compliance and cure rates.

## **Trial #2: Randomized Trial of Longer-Term Therapy for Symptoms Attributed to Lyme Disease**

Some patients may experience persistent symptoms after completing appropriate antimicrobial therapy for Lyme disease. This has been called post-Lyme disease syndrome or chronic Lyme disease, although in the medical community there is no agreement that these syndromes exist, and there is no understanding of why it occurs.

### Study Objectives / Purpose

This study aimed to determine whether longer-term antibiotic treatment of persistent symptoms attributed to Lyme disease leads to better outcomes than does shorter-term treatment.

### Brief Background

Previous randomized, clinical trials have not shown convincingly that prolonged antibiotic treatment has beneficial effects in patients with persistent symptoms

attributed to Lyme disease. A few small, placebo-controlled trials have shown positive effects for some outcomes only, such as fatigue. Most guidelines do not recommend antimicrobial therapy duration for longer than two to four weeks.

### Funding Sources

This study was funded by the Netherlands Organization for Health Research and Development ZonMw.

### Study Design and Methodology

This study was a randomized, double-blind, placebo-controlled trial.

### Patient Selection and Enrollment

Patients were included if they met the following criteria:

- Adults with borreliosis-attributed persistent symptoms (musculoskeletal pain, arthritis, arthralgia, neuralgia, sensory disturbances, or neuropsychological/cognitive disorders, with or without persistent fatigue)

IF either:

- Temporally related to an erythema migrans or otherwise proven symptomatic borreliosis
- Accompanied by a positive *B. burgdorferi* IgG or IgM immunoblot

Patients were excluded if they met any of the following extensive criteria:

- Known history of allergy/intolerance to tetracyclines, macrolides, hydroxychloroquine, or ceftriaxone
- Received greater than 5 days of antimicrobial therapy with activity against *B. burgdorferi* within the previous 4 weeks
- Presumed diagnosis of neuroborreliosis, requiring IV antimicrobial therapy
- Known diagnosis of HIV or other immune disorders
- Positive syphilis serology or signs of other spirochetal diseases
- Moderate or severe liver disease (ALP, ALT, or AST >3x ULN)
- Receiving and cannot discontinue cisapride, astemizole, terfenadine, barbiturates, phenytoin, or carbamazepine
- Currently enrolled on other investigational drug trials or receiving investigational agents
- Previously randomized into this study
- Severe physical or psychiatric co-morbidity that interferes with participation in the study protocol, including previous medical diagnosis of rheumatic conditions, chronic fatigue syndrome, or chronic pain conditions, as well as insufficient command of the Dutch language
- Co-morbidity that could (partially) account for symptoms (e.g., vitamin B12 deficiency, anemia, hypothyroidism)
- Child-bearing potential unwilling to use contraception methods other than oral contraceptives during study

## Interventions

All patients first received open-label intravenous ceftriaxone 2000 mg daily for 14 days. They were then randomized to receive one of the following three interventions:

- Oral doxycycline 100 mg twice daily PLUS placebo twice daily for 12 weeks
- Oral clarithromycin 500 mg twice daily PLUS hydroxychloroquine 200 mg twice daily for 12 weeks
- Oral double placebo twice daily for 12 weeks

#### Outcome Measures / Endpoints

The primary outcome measured was health-related quality of life at the end of the treatment period (week 14), as assessed by the physical component score of the RAND-36 Health Status Inventory. Secondary outcomes included: physical and mental aspects of health-related quality of life, fatigue, neuropsychological assessment, and physical activity.

#### Statistical Analyses

Statistical measures appropriately used in this study included: modified intention-to-treat, and analysis of covariance (ANCOVA) with sex and baseline SF-36 physical-component summary score as covariates.

#### Enrollment and Baseline Characteristics

86 subjects were randomized to the doxycycline group, 96 subjects were randomized to the clarithromycin plus hydroxychloroquine group, and 98 subjects were randomized to the placebo group. The population was almost exclusively white, and 87-91% of participants had received previous antibiotic treatment. Most subjects had current symptoms of: fatigue, arthralgia, neurocognitive symptoms, musculoskeletal pain, and sensory disturbances.

#### Summary of Primary and Secondary Outcomes

- The mean SF-36 physical-component summary score among all patients in the modified intention-to-treat analysis increased from 31.8 at baseline to 36.4 at the end of the treatment period ( $P < 0.001$ )
- At weeks 26, 40, and 52, the SF-36 physical-component summary score remained higher than the baseline score but did not change significantly from the score at the end of the treatment period
- None of the secondary outcome measures at the end of the treatment period differed significantly

#### Brief Summary of Authors' Main Discussion Points

- Prolonged antibiotic treatment (ceftriaxone followed by 12 weeks of either doxycycline or clarithromycin-hydroxychloroquine) did not lead to a better health-related quality of life than that with shorter-term treatment (ceftriaxone followed by placebo)

- At the 14-week visit, the mean SF-36 physical-component summary score had improved significantly from baseline regardless of the study-group assignment, but quality of life remained below that of the general population

### Authors' Conclusions

The authors concluded that 14 weeks of antimicrobial therapy does not provide clinical benefit beyond that with shorter-term treatment among patients who present with fatigue or musculoskeletal, neuropsychological, or cognitive disorders that are temporally related to prior Lyme disease or accompanied by positive *B. burgdorferi* serologic findings.

### Study Strengths

Efforts were made to verify patient adherence, utilizing pill counts, patient diaries, and Medication Event Monitoring System medication bottle caps – this is especially important due to the duration of therapy being studied. The patients were also followed for an extended period of time, 52 weeks after the start of the treatment period.

### Study Limitations

Again, unfortunately Lyme disease in Europe is caused by a different species of *Borrelia*, limiting the ability to extrapolate results to the United States population.

The study did not include a group that received only placebo, as it was deemed potentially unethical to withhold treatment from participants who may have an underlying infection, which is one of the unproven theories behind persistent Lyme symptoms. The study population may have unintentionally included patients with undiagnosed active *Borrelia* infection. Also, the cause of persistent symptoms associated with Lyme disease is ultimately unknown.

#### Applicability and Impact on Pharmacists / Healthcare Providers

Pharmacists are excellent advocates for antimicrobial stewardship, and this is an opportunity to educate both patients and providers about the lack of benefit seen with, as well as the significant adverse effects and risk associated with longer-term antibiotic use. There have been deaths documented as a result of unsuccessful long-term antibiotic use in an attempt to treat persistent symptoms associated with Lyme disease.

#### Conclusions and Recommendations

Appropriate antimicrobial treatment courses should correspond with current guidelines and therefore not exceed a maximum range of up to 28 days for severe cardiac or neurological manifestations of Lyme disease.

## **Role of the Pharmacist**

Pharmacists need to be able to counsel patients regarding medication side effects, and the importance of completing their antibiotic course. They can also educate patients on the signs and symptoms of unresolved illness (rash, fever, etc.), and offer guidance on when to contact their physician.

Pharmacists are also readily accessible to the public and can discuss with patients ways to prevent future tick bites. This is important for patients in endemic areas, as well as patients who have completed therapy for Lyme disease, as they are not immune to the disease and may contract it if they are bitten by an infected tick again.

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