# LYME DIS— EASE

**The Facts in Australia ::**

## WHAT PHARMACISTS NEED TO KNOW ABOUT LYME DISEASE IN AUSTRALIA

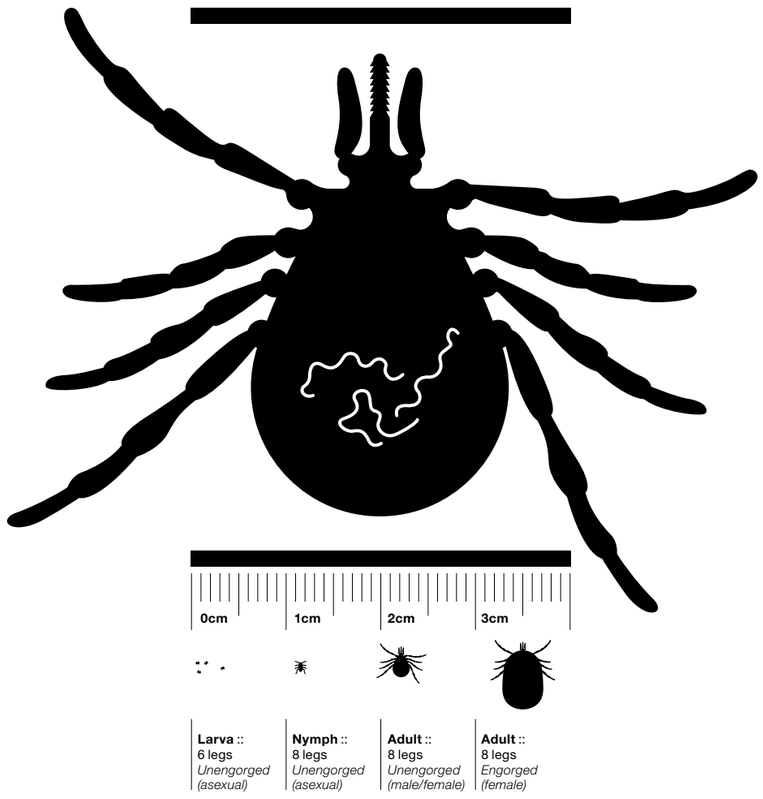
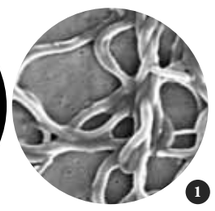



*Chart*: Comparison of tick sizes and life stages



Lyme Facts :: for :: Pharmacists



1

## WE WOULD LIKE TO PROVIDE YOU WITH MORE DETAILED INFORMATION ABOUT THE TREATMENT OF LYME DISEASE—

**We would like to provide you with more information regarding the treatment of Lyme disease (Lyme borreliosis), co-infections and other complicating factors.**

As awareness increases, more people will be presenting with a diagnosis of Lyme disease and will require multi-pharmacotherapies and close monitoring. This information is by no means a comprehensive document. Please contact the foundation so that we can refer you to the appropriate medical literature.

**TREATMENT**

Lyme disease, a bacterial infection transmitted by ticks, is treated with antibiotics. The earlier antibiotics are started, the better the outcome. The bacteria that causes Lyme disease belongs to a group called *Borrelia burgdorferi sensu lato*. The Borrelia bacteria exist in 3 different forms: spirochete, cell wall deficient and cyst. When the spirochete senses a hostile environment such as the presence of an antibiotic, it changes to a cell wall deficient or cyst form. It is critical that antibiotic treatment addresses all three forms *(Miklossy et al., 2008)*.

The following antibiotics are used: beta-lactam antibiotics e.g. amoxycillin or ceftriaxone for the spirochete form, doxycycline or macrolides for the cell wall deficient intracellular form and nitroimidazoles, such as metronidazole and tinidazole for the cyst form *(Burrascano, 2008)*. Prophylactic treatment after a tick bite, requires four weeks of treatment with doxycycline 100mg twice a day for adults and clarithromycin twice a day for children.

If the treatment is started three months post tick bite when Borrelia infections are considered as chronic, then three different antibiotics should be administered to address the three different forms of Borrelia (see above). Other pathogens (co-infections) delivered by the tick bite require treatment (see Table 1). Optimum duration of treatment depends on the severity of symptoms and the combination of co-infections.

### The Herxheimer reaction

It is important to be aware that during antibiotic treatment, endotoxins are released from dying Borrelia. As they accumulate the patient's symptoms worsen. This is known as the Jarisch-Herxheimer reaction. Minimising this reaction by fine-tuning antibiotic therapy is vital. The toxins released from Borrelia are both lipophilic and hydrophilic, the lipophilic toxins being much harder to remove.

### Detoxing

There are various ways of removing toxins. The lymph is a major organ of toxin elimination and supporting the lymphatic system is essential. Regular exercise related movements may help.

Lipophilic toxins can be removed by cholestyramine which can also bind to many drugs and fat soluble vitamins. It should be taken 2-4 hours after food, lipophilic medication and Vitamins A, E and D, otherwise reduced therapeutic effects and vitamin deficiencies may result.

Another important medication is Ursofalk (ursodeoxycholic acid). This medication prevents reabsorption of lipophilic toxins and bile accumulation associated with prolonged ceftriaxone therapy. Detoxing can also be addressed by using N-acetylcysteine, methyl-vitamin B12 and glutathione *(Burrascano, 2008)*.

### Complementary supplements

The onslaught of antibiotics removes gut flora so it needs to be supplemented using probiotics. As the dose of antibiotics increases, so should the dose of probiotics containing *Lactobacillus acidophilus*, *Lactobacillus casei* and *Bifidobacterium longum/lactis*. All three bacteria are needed to balance gut flora.

Borrelia bacteria does not require iron like other bacteria but manganese and zinc, and these minerals need to be supplemented. Zinc is also good for improving the immune response. The inflammatory reaction is stimulated by toxins and by the bacteria itself. TNF-alpha (tumor necrosis factor-alpha), IL-6 (interleukin-6), IL-8 (interleukin-8) are produced and antioxidants like vitamins A, C, E and coenzyme Q10 help to reduce tissue damage.

Pharmacists have a vital role in managing medications, probiotics, antioxidants, vitamins and minerals of Lyme disease patients, and most importantly deciphering drug interactions due to multi-pharmacotherapy.

Excellent guidelines for treating Borrelia infections have been written by Joseph Burrascano (see references).

**AUSTRALIAN CHRONIC LYME DISEASE**

Australian chronic Lyme disease has a marked neurological presentation (neuroborreliosis), so familiarity with the CNS anatomy and attributing damage to different CNS nerves is important.

Neurological damage may occur by bacterial invasion of the nervous system causing degeneration, wasting of muscles, nerves and other body tissues. Damage can also occur by inflammation of the blood and lymph vessels (vasculitis) which decreases blood supply to the tissues and causes cell death. In addition, Borrelia produces neurotoxins such as quinolinic acid that also damage the nervous system.

The 3 most common neurological symptoms, (known as Bannwarth syndrome) include:
**1.** Cranial nerve damage
**2.** Nerve root inflammation *(radiculoneuritis)*
**3.** Meningitis

Cranial nerve palsy is a common symptom of neuroborreliosis. There are 12 cranial nerves and symptoms include:
**1.** Olfactory : altered smell
**2.** Optic nerve : loss of vision
**3.** Oculomotor : eyelids may droop, eyeball may deviate outwards
**4.** Trochlear : eyeball may rotate upwards and outwards, double vision
**5.** Trigeminal : pain or numbness in parts of the face, forehead, jaw, teeth, difficulty chewing, jaw paralysed
**6.** Abducens : eyes deviate outwards, excessive squinting
**7.** Facial nerves : Bell's palsy, eye droop, hearing loss on the same side, tooth, ear, jaw pain, disruptions of mucous membranes, loss of taste
**8.** Vestibulocochlear : hearing disturbances, balance problems, vomiting, dizziness
**9.** Glossopharyngeal : tongue, abnormal taste sensations, difficulty swallowing, paralysis of glottis
**10.** Vagus : dysfunction of the muscles in the throat, shoulders and back may create difficulty in swallowing or talking, drooping shoulders, palpitations, breathing difficulties, persistent cough, paralysis of the glottis, vocal cord spasms, paralysis
**11.** Spinal Accessory : disrupted function of or paralysis of the upper back and neck, inability to hold or rotate the head
**12.** Hypoglossal : tongue paralysis, larynx, speech, swallowing difficulties.

These nerves can also affect the liver, intestines, spleen, kidney, thyroid, testis or ovaries. Other nerve involvement in neuroborreliosis may include diminished reflexes, sharp shooting pain that radiates down the arms, legs and back, areas of numbness, tingling, prickling, poor muscle coordination, muscle weakness or paralysis, muscle twitching, movement disorders and gait problems.

The seriousness of symptoms can produce depression. The spread of the infection to the brain and spinal cord can produce meningitis, encephalopathy and psychiatric symptoms.

With a neurological presentation of Lyme disease as seen in Australia, patients can be misdiagnosed with motor neurone disease (MND) /amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), Parkinson's disease, Alzheimer's disease, myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS), autism, fibromyalgia and arthritis. This usually results from doctors being unfamiliar with Lyme disease and testing being inadequate.

**IS LYME DISEASE CONTAGIOUS?**

### Sexual transmission

Like syphilis, the Lyme bacterium is a spirochete and can move in viscous fluid like semen due to its internal flagellum. In addition, being a micro-anaerobic bacteria and growing optimally at 32°C, the testis is an ideal place for incubation and transmission *(Stricker et al., 2004)*.

### In-utero transmission

The risk to foetal development in Lyme disease is greatest in the first trimester. Adverse effects on the foetus include retarded growth, respiratory distress, eye problems, brain infection, heart abnormalities and damage to other organs. Other less common effects include miscarriage, foetal malformations, and early infant death *(MacDonald et al., 1987; Weber & Burgdorfer, 1994; Hercegova et al., 1996; Geber et al., 1996; Schlesinger et al., 1985)*.

### Lactation

In theory Lyme disease may be transmitted through breast milk as Borrelia has been found in breast milk *(Schmidt et al., 1995)*.

**LYME DISEASE TESTING**

Australia employs a two-tier system:

### ELISA

The initial test, an ELISA is based upon the detection of patients' antibodies against Borrelia proteins. Indirect labeling results in amplification and visualisation of the antigen antibody reaction.

False negative ELISA results may be due to a unique Australian strain which the kits cannot detect as it is designed for the American or the European species. Another reason is the antibodies bind to Borrelia in vivo and there are no free antibodies to bind to the Borrelia proteins in the ELISA test *(Tunev et al., 2011)*.

Another complication is that patients are immune suppressed by Borrelia and are not making antibodies or antibodies made are of low affinity. A negative ELISA does not necessarily mean you do not have Lyme disease. Ultimately Lyme disease diagnosis should be based on clinical symptoms *(Tunev et al., 2011)*.

### Western Blot

If the person's ELISA is positive then a Western Blot *(Immunoblot)* test is performed as the second tier. This is relatively more sensitive as antibodies to specific Borrelia proteins are visualised as bands. There are 15 possible bands and the most common bands are for flagellin antigen (41kDa), outer surface protein A (31kDa) and outer surface protein C (23kDa).

Western Blot can be done for IgM, and according to Centers for Disease Control USA (CDC) two bands are sufficient to confirm Lyme disease. For IgG Western Blot, five bands are needed to confirm Lyme disease.

The CDC criteria is excessively stringent and up to 90% of patients with Lyme are missed. The International Lyme and Associated Diseases Society (ILADS) states that several studies have shown that sensitivity and specificity for both IgM and IgG western blot range from 92-96% when only 2 specific bands are positive *(www.ilads.org/files/ILADS_Guidelines.pdf)*.

**There is an urgent need to identify the Australian genospecies of Borrelia to improve testing in Australia.**

**CO-INFECTIONS**

Ticks are nature's 'dirty needles'. Ticks transmit not only Borrelia bacteria but also other co-infections such as Babesia, Bartonella, Anaplasma, Ehrlichia, Rickettsia, Mycoplasma and possible virus pathogens.

### Babesia

Around 70% of people with Lyme disease also have babesiosis *(Schaller, 2008)*. Babesia is also immunosuppressive. It is a protozoa causing malaria-like illness. There are many genospecies and include *B. microti*, *B. divergens* and *B. duncani*. Babesia invade and infect red blood cells and lyse them at regular intervals giving raise to sweat attacks. Babesia may also be acquired by blood transfusion *(Gubernot et al., 2009)*.

Symptoms can appear one week after a tick bite but may appear 6 weeks later. They can range from asymptomatic to severe (sometimes fatal). Symptoms of mild infection may include fever, fatigue, muscle aches, headache, joint pain, nausea, and stomach pain. Severe illness may include drenching malaria-like chills and sweats, severe headaches, intravascular coagulation, balance problems and shortness of breath. Borrelia and Babesia act synergistically as lysing red blood cells, creating an anaerobic microenvironment for Borrelia.

As for malaria, treatment involves artemisinin, atovaquone and Malarone (atovaquone and proguanil) (see Table 1). CoQ10 can possibly diminish the action of atovaquone and is contraindicated. Atovaquone needs to be taken with a fatty meal to increase absorption. The length of time Babesia is treated depends on the intensity of symptoms and degree of immunosuppression.

### Bartonella

Bartonella is an aerobic bacteria. It was first recognised in 1889 as cat-scratch disease and in World War 1 as trench fever. The species involved are *B. henselae* and *B. quintana*. It can exist in intracellular and extracellular forms. Symptoms include swollen lymph glands, low-grade fever, malaise, fatigue, enlarged spleen, pharyngitis and synovitis. These symptoms are similar to other co-infections.

Treatment with ciprofloxin 500mg twice a day is recommended (see Table 1). Atovaquone inactivates ciprofloxin, so it is important to treat Bartonella before Babesia. A side effect of ciprofloxin is tendon problems, so advise on having high-dose vitamin C and magnesium to prevent tendon rupture *(Burrascano, 2008)*.

### Ehrlichia/Anaplasma

Ehrlichia/Anaplasma is a small gram-negative bacteria that invades white blood cells and causes human granulocytic ehrlichiosis (HGE) and human monocytic ehrlichiosis (HME). Thrombocytopenia and elevated liver enzymes are seen in acute infection. Concomitant with Borrelia infection, there is usually persistent leucopenia, headaches, myalgia and ongoing fatigue. Ehrlichiosis symptoms are similar to borreliosis and often difficult to differentiate. Treatment is with doxycycline 200mg daily (see Table 1). The length of treatment depends on the severity of symptoms.

### Rickettsia

The existence of Rickettsia in Australian ticks, fleas and lice is well documented and the pathogenic species have been identified as *R. typhi*, *R. australis*, *R.honei* "marmioni", *R. honei*, and *Orientia tsutsugamushi (Unsworth et al., 2007)*. Rickettsia are intracellular parasites and spread via the bloodstream to infect vascular endothelium and multiply only in the cytoplasm of the host cell. Symptoms include fever, severe malaise, memory loss, muscular weakness, macupapular rash and tachycardia. Treatment of choice is doxycycline.

### Mycoplasma

Mycoplasma are very small cell wall deficient bacteria and there are over 100 species. Mycoplasma can be parasitic or saprotrophic (feeds on dead cell debris). Mycoplasma requires sterols for the stability of its cell membrane, which it acquires from the host's body supply. Important species with borreliosis are *M. fermentans* and *M. pneumoniae.*

Symptoms depend on the species e.g. pneumonia for *M. pneumoniae* and *M. fermentans* tend to predominate in neuroborreliosis. Treatment involves doxycycline, azithromycin or fluoroquinolones (eg. ciprofloxin) and hydroxychloroquine to kill the different stages of mycoplasma (see Table 1).


**Acknowledgements:**

We would like to thank:
— Judith Miklossy and her colleagues for providing microscopic images of Borrelia.
— Ryan F. Relich, Mitchell F. Balish, Miami University Center for Advanced Microscopy and Imaging for providing microscopic images of mycoplasma.
— Centers for Disease Control USA for providing images of Ehrlichia, Borrelia, Babesia and Rickettsia.




*Images*: **1.** Borrelia (see above) **2.** Babesia **3.** Bartonella **4.** Ehrlichia **5.** Rickettsia **6.** Mycoplasma

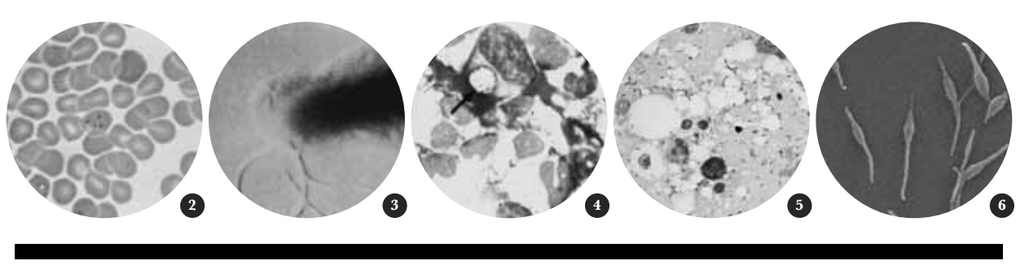



**TABLE 1: SUMMARY OF BORRELIA, CO-INFECTIONS, MYCOPLASMA and VIRAL PATHOGENS**

| Pathogen | Disease | Treatment | Notes |
|---|---|---|---|
| **Borrelia** *B. burgdorferi*, *B. afzelii*, *B. garinii* Spirochete form. Extracellular, capable of intracellular. | Borreliosis | Beta lactam antibiotics eg: amoxycillin, ceftriaxone or cefuroxime. | Very mobile, spiral and drill capabilities allow penetration into dense tissue. Rapidly converts to other forms, especially in the presence of antibiotics. |
| **Borrelia** Cell wall deficient form (L-form). | Borreliosis | doxycycline, azithromycin or clarithromycin. | Lack of cell wall makes it difficult for immune system to target. |
| **Borrelia** Cyst form. Intracellular or extracellular. | Borreliosis | metronidazole, tinidazole or hydroxychloroquine. | The non-motile dormant form can survive certain antibiotics. Converts back to spirochete when conditions are favourable. |
| **Babesia** Protozoa *B. microti*, *B. duncani*, *B. divergens* | Babesiosis, a malaria-like illness. | atovaquone, atovaquone and proguanil (Malarone), (contraindicated with CoQ10) + azithromycin, clindamycin + quinine; Alternative: artemisinin (Blackmores), or artemether + lumefantrine (Riamet™). | Approximately 70% of Lyme patients have Babesiosis. Infects red blood cells and lyse them at regular intervals. Babesia creates anaerobic micro-environment for Borrelia proliferation. Dark urine. |
| **Bartonella** Gram-negative *B. henselae*, *B. quintana* | Bartonellosis (cat-scratch disease, trench fever) | erythromycin or ciprofloxin. N.B. atovaquone can inactivate ciprofloxin so need to treat Bartonella before Babesia. | Note: ciprofloxin can cause tendon problems (use high dose vitamin C & magnesium to prevent tendon rupture). Pain in soles of feet. |
| **Ehrlichia/ Anaplasma** Gram-negative *Erhlichia chaffeensis*, *Anaplasma phagocytophilum* | Human Monocytic Ehrlichiosis, Human Granulocytic Ehrlichiosis | doxycycline or rifampicin. | Infects white blood cells. A persistent leucopenia is often seen. Thrombocytopenia and elevated liver enzymes observed in acute infection. |
| **Rickettsia** Gram-negative *R. honei*, *R. australis*, *R. typhi*, *Orientia tsutsugamushi* | Flinders Island spotted fever, Queensland tick typhus, Murine Typhus, Scrub typhus | doxycycline | Maculopapular skin rash, severe headache (especially behind eyes). |
| **Mycoplasma** Lacks a cell wall *M. fermentans*, *M. pneumoniae* | Mycoplasmosis | doxycyline, azithromycin, clarithromycin, hydroxychlorooquine or fluoroquinolones. | Over 100 species. Very small bacterium. Lacks a cell wall. Difficult to eliminate and slow growing. Feeds on the host's cholesterol supply. |
| **Viral Pathogens** HHV-6, EBV, CMV | | famciclovir, valaciclovir, ganciclovir or anti-retrovirals eg. zidovudine, ritonavir. | HHV-6 human herpes virus. EBV Epstein-Barr virus. CMV cytomegalovirus. |

**Recognising. Understanding. Caring.**


Karl McManus Foundation for Lyme Disease Research & Awareness
PO Box 3129, North Turramurra, NSW 2074




Design Aerofoil :: www.aerofoil.com.au
Print Green and Gold :: www.greenandgold.com.au
Paper K.W.Doggett Fine Paper :: www.kwdoggett.com.au


**Karl McManus Foundation ::**
*for Lyme Disease Research and Awareness*

KARL MCMANUS FOUNDATION

**References:**


*Burrascano JJ (2008)*, Advanced Topics in Lyme disease: Diagnostic hints and treatment guidelines for Lyme and other tick borne illnesses. 16th Edn. http://lymediseaseresource.com/BurrGuide2008.pdf

*Gerber MA, Shapiro ED, Burke CS, Parcells VJ & Bell GL (1996)* Lyme disease in children in southeastern Connecticut. Paediatric Lyme Disease Study Group. N. Eng. J. Med. 24, 1720-1724

*Gubernot DM, Lucey CT, Lee KC, Conley GB, Holness LG & Wise RP (2009)* Babesia infection through blood transfusions: reports received by the US Food and Drug Administration, 1997-2007. Clin Infect Dis. 48:1, 25-30

*Hercogova J, Hulinska D, Ziwny J & Janovska D (1996)* Erythema migrans during pregnancy: Study 0f 35 womenn VII International Congress on Lyme Borreliosis SanFrancisco, CA Uniof California, Berkeley p 172

ILADS Guidelines: www.ilads.org/files/ILADS_Guidelines.pdf

*Mac Donald, A Benach J. & Burgdorfer, W. (1987)* Still-birth following maternal Lyme disease. New York State Journal of Medicine 87, 615-616

*Miklossy J, Kasas S, Zur AD, McCall S, Yu S & McGeer PL (2008)* Persisting atypical and cystic forms of *Borrelia burgdorferi* and local inflammation in Lyme neuroborreliosis. J. Neuroinflamm. 5:40, doi:10.1186/1742-2094-5-40

*Schaller J (2008)*, Babesiosis, Hope Academic Press Publishing

*Schlesinge PP, Duray B, Burke A, Steere A & Stillman T (1985)* Maternal-fetal transmission of the Lyme disease spirochete BB. Ann Internal Medicine. 103, 67-68

*Schmidt BE, Aberer C, Stockenhuber H, Klade F et al (1995)*, Detection of BB in the urine and breast milk of patients with LB. Diagn. Micro. Infect. Dis 21, 121-128

*Strasheim C (2009)* Insights into Lyme disease Treatment, Bio Med Publishing

*Stricker R.B, Moore DH & Winger EE. (2004)* Clinical and immunologic evidence of transmission of Lyme disease through intimate human contact. J. Invest. Med. 52, S151

*Tunev S, Hastey C, Hodzic E, Feng S, Barthold S & Baumgarth N (2011)* Lymphadenopathy during LB is caused by spirochete migration induced B cell activation. PLos Pathogens. 7: 5 1-4

*Unsworth NB, Steno J, Faa AG & Graves S(2007)* Three rickettsioses, Darnley Island, Australia. Emerging Infectious Diseases. 13:7, 1105-7

*Weber K & Burdorfer W (1994)* The cradle of Lyme Borreliosis J. Spirochetal and Tick borne Disease. 1, 35-36


Pharmacists :: thanks :: for your time