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AN AUSTRALIAN GUIDELINE ON THE DIAGNOSIS OF OVERSEAS-ACQUIRED LYME DISEASE/BORRELIOSIS

Gary D Lum, Jennie R Hood, Phil Wright

Executive summary

While classical Lyme disease cannot be acquired in Australia, patients may present who have travelled through endemic areas. Lyme disease is prevalent in north east United States of America, parts of Europe including Germany, Austria, Slovenia and Sweden as well as parts of the United Kingdom. Lyme disease can also be found in Russia, Japan and China. For patients who present with no history of overseas travel but with a tick bite and systemic symptoms, e.g. fever, contact with your specialist microbiologist to discuss test referral and with your infectious diseases physician to discuss antimicrobial treatment of tick-borne infections in the Australian context is advised.

Lyme disease should be considered in patients presenting with a history of tick bite from one of these areas along with a fever and mild influenza-like symptoms. An annular rash, erythema migrans may be present in 70%–80% of patients presenting with Lyme disease. Other manifestations of Lyme disease can occur. For example, Lyme neuroborreliosis can manifest as meningoradiculoneuritis, meningitis, cranial neuritis (predominately involving the facial nerve), brachial plexus neuritis, and mononeuritis; Lyme carditis can manifest with palpitations, chest discomfort, shortness of breath, dizziness on exercise or syncope; and rheumatological Lyme disease can present with arthralgia and myalgia. Rheumatological presentations are more common with north American acquisition and neurological presentations with European acquisition.

If Lyme disease is being considered, patients should be referred for Lyme disease serology to your regular approved pathology practitioner.

The testing follows a two-tiered approach involving a screening immunoassay and a confirmatory immunoblot. If you have concerns or questions about the testing please contact your approved pathology laboratory's specialist microbiologist.

While this guidance document is focussed on the diagnosis of overseas-acquired Lyme disease in Australia, treatment advice can be found on the [Infectious Diseases Society of America web site](http://www.idsociety.org/ViewAllLyme/)

(<http://www.idsociety.org/ViewAllLyme/>). Should you require further advice please make contact with an infectious diseases physician.

Figure 1 shows the recommended steps for diagnosing overseas-acquired Lyme disease in Australia.

Purpose

This document is a diagnostic clinical aid* for medical practitioners in Australia who are unfamiliar with Lyme disease acquired overseas.†

An Australian Lyme disease-like syndrome (ALDLS) case description is not part of this document. The use of the term Australian Lyme disease-like syndrome is not a formal acknowledgment or designation of a new disease in Australia. If ALDLS can be better characterised as a chronic debilitating multi-organ illness affecting some Australians a separate ALDLS description can be written.

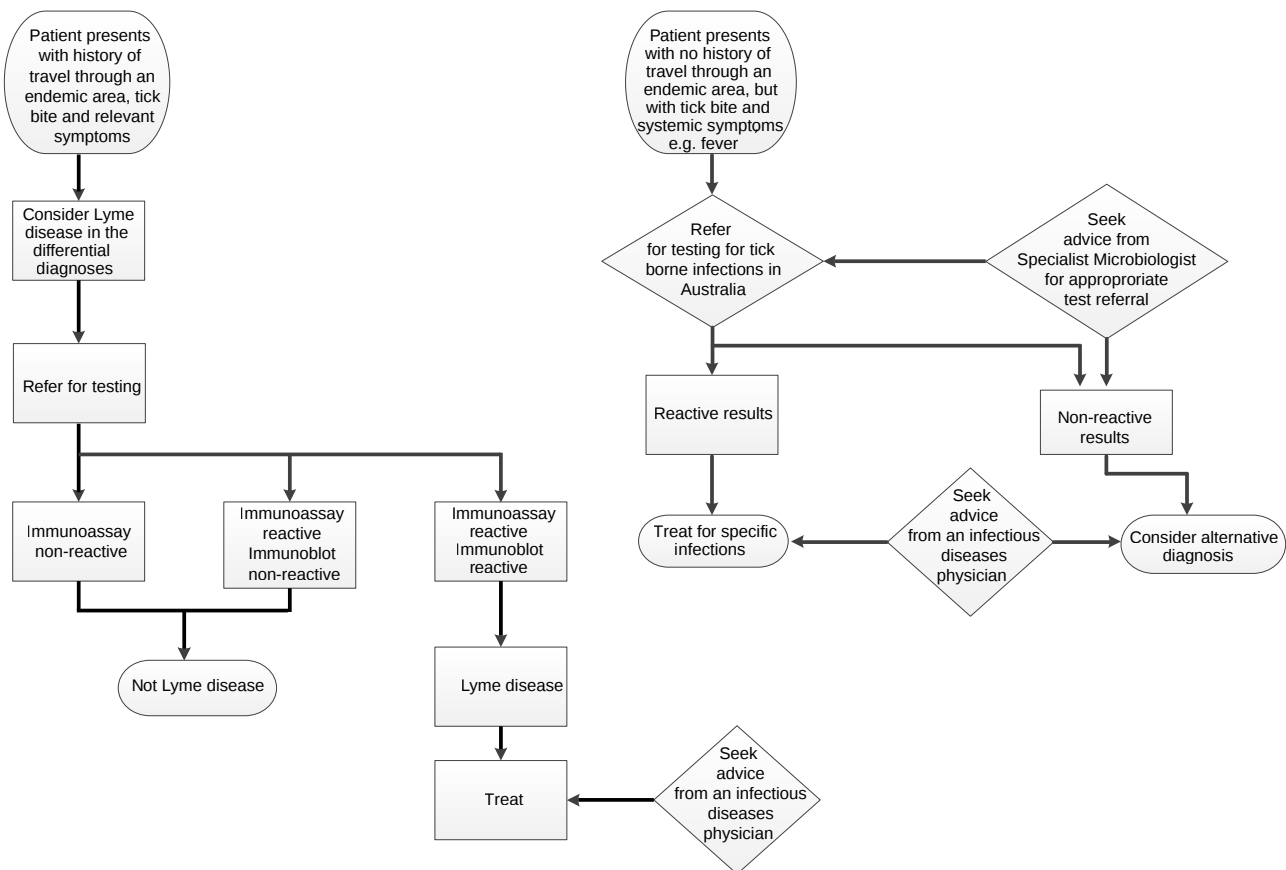
This diagnostic guide for overseas-acquired Lyme disease is not a national disease surveillance document. Lyme disease is not a notifiable disease in Australia. This document does not address chronic Lyme disease, relapsing fever or Lyme disease co-infections.‡ This guide is not a comprehensive 'text book' description of the natural history of an infection. Details on the epidemiology and *in vitro* diagnostic device specifications can be obtained elsewhere. Specific advice on the specifications of *in vitro* diagnostic assays used in Australia should be sought from the responsible specialist microbiologist or medical laboratory scientist offering Lyme disease testing.

Input has been sought from members of the Diagnostic Pathway Working Group of the Chief Medical Officer's Clinical Advisory Committee

* The case definition is for guidance rather than being a prescriptive standard.

† Patients and their advocates have reported that some Australian registered medical practitioners are not considering a diagnosis of Lyme disease in patients who have travelled to overseas endemic areas.

‡ For example infections caused by *Babesia*, *Anaplasma*, *Bartonella* and *Ehrlichia*.

Figure 1: Flow chart for an Australian diagnostic guideline for overseas acquired Lyme disease

on Lyme disease and was discussed at the Lyme Disease Treatment Round Table held on Tuesday 27 May 2014. This guide has been considered by the Public Health Laboratory Network and the Communicable Diseases Network Australia. It has been endorsed by the Australian Health Protection Principal Committee on 13 August 2015.

As a guidance document, laboratory diagnostic testing is required for 2 reasons: 1. For overseas acquired infection by the genogroup *Borrelia burgdorferi* sensu lato, unless the clinician is familiar with the pathognomonic erythema migrans (EM) rash, it is clinically safer to obtain supportive evidence of infection through diagnostic testing, and 2. diagnostic laboratory support is preferred for patients presenting with non-specific signs and symptoms of a disease or syndrome, notwithstanding the limitations of diagnostic tests.

Lyme disease / borreliosis

An indigenous causative microorganism is yet to be found in Australia. This case definition can be applied to patients with Lyme disease acquired from endemic areas overseas.

Confirmed case

The diagnosis of overseas-acquired Lyme disease in Australia should rest on a careful medical history and objective clinical findings with the support of appropriate *in vitro* diagnostic tests. Laboratory support is essential because of the non-specific nature of many clinical manifestations, especially when the diagnosis is made in a non-endemic area.

A confirmed case requires laboratory definitive evidence AND clinical evidence AND epidemiological evidence.

Laboratory definitive evidence

Culture of *Borrelia* bacteria[§] from clinical specimens offers the best confirmation of active infection. However, due to the low numbers of viable spirochaetes usually present in patient biopsies and the fastidious nature of *Borrelia* species, the sensitivity of culture is poor.^{1,2,3} The inability to isolate an organism does not exclude active infection.¹ Relevant *Borrelia* species can be recovered from various tissues and body fluids including: biopsy and lavage specimens of EM skin lesions, biopsy specimens of acrodermatitis chronica atrophicans

§ Known to cause Lyme borreliosis in endemic areas

(ACA) skin lesions, biopsy specimens of borrelial lymphocytoma skin lesions, cerebrospinal fluid (CSF) specimens, synovial fluid and blood specimens.^{3,4} There have also been reports of recovery of relevant *Borrelia* species from other tissues such as cardiac tissue.^{3,5}

OR

Detection of relevant *Borrelia* species by nucleic acid amplification tests (NAT) (e.g. polymerase chain reaction (PCR)) taken from skin biopsies of EM or ACA skin lesions or appropriate body fluid samples of blood, CSF or synovial fluid (depending on clinical manifestations).^{3,4} The use of urine-PCR has been investigated by several groups, but results are contradictory, therefore PCR on urine is not recommended for routine diagnosis.^{1,4}

OR

Serological evidence by two tiered testing. An immunoblot (IB) should not be performed without a reactive immunoassay screening result. A positive diagnosis can only be achieved with a reactive screening immunoassay and sufficient number of reactive bands in an IB.

Serological evidence requires both:

- the presence of IgM (acute phase[¶]) or IgG (convalescent phase) detected by an immunoassay** using recombinant antigen. (In the convalescent period, a reactive IgM and a nonreactive IgG should be regarded as a falsely positive IgM result.)

AND

- the presence of IgG (convalescent phase) detected by an IB using recombinant antigen or whole cell preparations and fulfilling criteria for a positive result. Although IgM IBs are available, repeat testing for IgG by IB on a convalescent sample is advised.

Testing should be performed in a laboratory that has Lyme disease testing in its scope of accreditation and which is compliant with *AS ISO 15189 Medical laboratories — Particular requirements for quality and competence* or in nationally accredited laboratories in the location where the patient was infected. Commercial serological assays used in Australian laboratories with AS ISO 15189 medi-

cal testing accreditation are suitable for testing for Lyme disease acquired overseas in endemic regions. Consideration should be given to storing positive serum specimens for research and quality assurance purposes.

Clinical specimens that produce repeatedly equivocal results, indeterminate results and results from laboratories without AS ISO 15189 medical testing accreditation should be considered cautiously and expert advice from a specialist microbiologist should be obtained. It may be necessary to refer patient specimens to a suitably certified laboratory such as the US Centers for Disease Control and Prevention.

Clinical evidence

For the purposes of this case definition, a history of overseas travel to areas where Lyme disease/borreliosis is endemic is required when assessing a patient's clinical presentation. For a diagnosis of Lyme disease to be considered the patient must have been exposed to ticks, however, a history of documented tick bite is not essential because many tick bites go unnoticed.¹

The clinical presentation of borreliosis depends on the different stages of the disease. It has also been demonstrated that different genospecies exert different organotropic and pathogenic potential.^{6,7} For the purpose of this case definition three broad disease stages are recognised: early Lyme disease, early disseminated Lyme disease and late Lyme disease. Not all stages need to appear, stages may also overlap and the infection may also be asymptomatic.⁸ Examples of the different clinical manifestations of the three most common genospecies (*B. burgdorferi* s.s., *B. afzelii* and *B. garinii*) are provided in the Appendix.

Early Lyme disease

Early Lyme disease generally occurs within several days (but may be up to 4 months) after a tick bite and may include symptoms such as the presence of an isolated EM rash (Figure 2), undifferentiated febrile illness and/or influenza-like symptoms (including fatigue and myalgia) or patients may be asymptomatic.⁹

EM is a characteristic expanding rash (usually larger than 5 cm) that may develop 3 days to 16 weeks after a tick bite and resolves spontaneously in a few weeks or months.⁸ The rash is present in 70%–80% of infected persons. The rash begins at the site of the tick bite as a red macule or papule, rapidly enlarges and sometimes develops central clearing but is often homogenous.^{1,7} The advancing edge is typically distinct and is often intensely

¶ Specific IgG is usually detectable 4 to 6 weeks after infection, although to determine a definite change in IgG levels a minimum of 3 months may be necessary to determine a change when tested in parallel.

** A non-reactive immunoassay should be regarded as a negative result.

coloured but not markedly elevated.¹⁰ The duration of the rash is usually dependent on the infecting genospecies but will last approximately 4 to 14 days^{9,11} Haemorrhagic or non-migrating forms have occasionally been observed.¹² Erythematous lesions occurring within a few hours after a tick bite represent hypersensitivity reactions and do not qualify as EM.¹ In endemic areas, EM is pathognomonic for infection.

Figure 2: Erythema migrans rash



Image source : US Centers for Disease Control and Prevention Public Health Image Library; Photo by James Gathany.

Early disseminated Lyme disease

A few weeks to months after the initial infection, several organs may become affected, usually due to haematogenous spread.^{7,8}

Lyme neuroborreliosis (LNB) is usually an acute disease (but can have chronic presentation), which develops within 1–12 weeks (mostly 4–6 weeks) after a tick bite.^{1,13} Neurological features include meningoradiculoneuritis, meningitis, cranial neuritis (predominately involving the facial nerve), brachial plexus neuritis, mononeuritis, and rarely encephalitis, myelitis and cerebral vasculitis. These manifestations may occur separately or in association.^{1,8,13,14} For a reliable diagnosis of LNB, indicative clinical neurological manifestations must be associated with inflammatory CSF pleocytosis and proof of intrathecal production of *Borrelia*-specific antibodies (IgG and/or IgM). Some commercially available serological assays are validated to test CSF specimens.

CSF PCR and CSF culture may be corroborative if symptom duration is less than 6 weeks when *B. burgdorferi* antibodies may be absent.¹³

Lyme carditis usually manifests as varying degrees of transient atrioventricular defects which may result in the following symptoms: palpitations, chest discomfort, shortness of breath, dizziness on exercise, or syncope. Other features can include arrhythmias, (myo)pericarditis, and heart failure.^{8,14}

Multiple EM-like lesions are common with some genospecies but uncommon with others. Borrelial lymphocytoma can appear in all stages but is most often observed during this stage.⁸

Arthralgia and myalgia signify early musculoskeletal involvement. Frank arthritis and myositis are occasionally observed. Regional lymphadenopathy and generalised lymphadenopathy may develop.⁸ Joint involvement is common in North America and less common in Europe.

Other features of this stage can include eye disorders (such as uveitis, papillitis, keratitis and episcleritis), hepatomegaly, hepatitis and rarely, a dry cough and testicular swelling.^{1,8}

Late Lyme disease

Late organ involvement may occur many months to years after infection and manifestations are primarily rheumatological and neurological.⁷ Chronic fatigue is also commonly reported.

With some genospecies, recurrent brief episodes of monoarticular or oligoarticular arthritis are common especially in the large joints.^{8,14} ACA is associated with certain genospecies, is almost exclusively seen in adults (predominantly women) and mainly affects the extensor surfaces of the extremities.^{1,14}

Long term progressive Lyme encephalitis and encephalomyelitis are extremely rare even in areas of high endemicity in the United States of America (USA) and in Europe. Manifestations can be highly variable depending on the localisation of inflammatory foci in the brain. The course is typically chronic progressive and spasticity and cerebellar symptoms are often prominent clinical features. Also on rare occasions cerebral vasculitis, myositis, a dermatomyositis-like syndrome, reactive hyperplasia of the bone marrow, keratitis, and dilated cardiomyopathy may be present independently or associated with ACA.⁸

Impaired cognitive function following treated Lyme borreliosis may also be observed (such as memory problems, poor concentration, difficulties in formulating ideas and difficulties in word find-

ing), but it is difficult to attribute these symptoms directly to *Borrelia* infection or indirectly through effects of systemic infection or other toxic metabolic factors.^{15–17} Patients with Late Lyme disease invariably have measurable serum specific antibodies. Post treatment late Lyme disease is not the same as chronic Lyme disease. Chronic Lyme disease is a controversial diagnosis and refers to ongoing active infection. Evidence for active long term infection remains controversial and is not widely accepted.

Epidemiological evidence

Epidemiological context is important. Determining a travel history and tick exposure prone activities are essential. The likelihood of Lyme disease increases as the probability of a tick bite increases in a geographically endemic area (particularly wooded, brushy, or grassy habitats). Endemic areas can be defined as those with established populations of vector ticks and evidence of enzootic transmission of relevant *Borrelia* species between the tick and the resident animal population.

In the USA, 13 states in the north east, where *Ixodes scapularis* is prevalent, account for 95% of reported cases; these states include Connecticut, Delaware, Maine, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey, New York, Pennsylvania, Vermont, Virginia, and Wisconsin.

In Europe, the regions with the highest prevalence include Germany, Austria, Slovenia, and Sweden (Figure 3). Lyme disease has been also diagnosed in the United Kingdom.

Lyme disease can also be acquired in Russia, Japan, and China.

Epidemiological evidence will be reviewed for an Australian context should an indigenous organism and its vector be identified.

Suspected case^{††}

The presence of supporting laboratory evidence^{‡‡} AND epidemiological evidence without signs and symptoms consistent with early Lyme disease^{§§} (and no alternative explanation/diagnosis)

OR

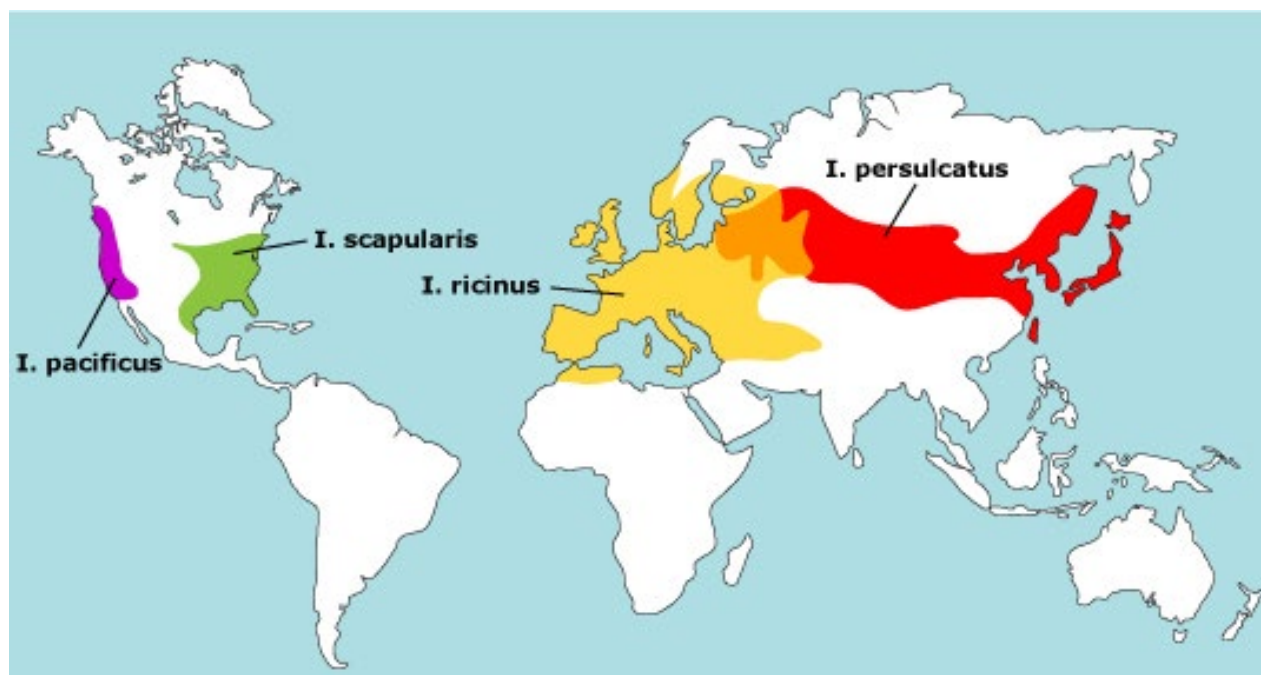
An EM rash AND epidemiological evidence (as defined above) (and no alternative explanation/diagnosis). Whilst this clinical manifestation may be pathognomonic in endemic countries unfamili-

^{††} Requires *in vitro* diagnostic testing to be performed in an AS ISO 15189 compliant laboratory.

^{‡‡} Positive nucleic acid amplification test results or reactive serological test results.

^{§§} For example, when there is history of a tick bite in an endemic region and Lyme disease testing has been requested and agreed.

Figure 3: Geographical distribution of the *Ixodes* tick vectors of the spirochetes that cause Lyme disease



Source: Eisen L, Lane RS. Vectors of *Borrelia burgdorferi* sensu lato. In: Lyme Borreliosis Biology, Epidemiology and Control, Gray JS, Kahl O, Lane RS, et al (Eds), CABI Publishing, Wallingford, Oxon, UK 2002. p. 91. Copyright ©2002 CAB International, Wallingford, UK.

arity with the presentation in Australia warrants laboratory confirmation (culture or PCR of the tissue) or more usually, antibody testing on a convalescent sample.

OR

Manifestations of LNB without CSF pleocytosis (including CSF not collected) and indeterminate laboratory results^{¶¶} AND epidemiological evidence (and no alternative explanation/diagnosis)

OR

Manifestations of rheumatological Lyme disease and indeterminate laboratory results AND epidemiological evidence (and no alternative explanation/diagnosis).

Treatment guidance

While this guidance document is focussed on the diagnosis of overseas-acquired Lyme disease in Australia, treatment advice can be found on the Infectious Diseases Society of America web site (<http://www.idsociety.org/viewalllyme>). Should you require further advice please make contact with an infectious diseases physician. Australian infectious diseases physicians receive training that includes the management of classical Lyme disease.

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¶¶ Non-reactive serological test results in CSF and equivocal or indeterminate serology results from serum specimens.

Appendix

Examples of different clinical manifestations of *Borrelia burgdorferi* s.s., *B. afzelii* and *B. garinii*

Certain clinical manifestations can occur more often with certain genospecies. The Appendix provides an indication of what symptoms are more likely to be associated with which genospecies.

Author details

Dr Gary D Lum, Medical Advisor, Medical and Scientific Advisory Unit

Dr Jennie R Hood, Medical and Scientific Advisory Unit

Mr Phil Wright, Zoonoses, Foodborne and Emerging Infectious Diseases

Office of Health Protection, Australian Government Department of Health, Woden, Australian Capital Territory

Corresponding author: Dr Gary D Lum, Medical Advisor, Medical and Scientific Advisory Unit, Office of Health Protection, MDP 14 GPO 4898, CANBERRA ACT 2601. Email: Gary.Lum@health.gov.au

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Appendix: Symptoms associated with *Borrelia* disease, by genospecies

Symptoms	<i>Borrelia burgdorferi</i> s.s.	<i>Borrelia afzelii</i>	<i>Borrelia garinii</i>
Erythema migrans	✓	✓	✓
Multiple erythema migrans	✓		
Lyme neuroborreliosis	Can occur		✓
Lyme carditis	✓	Rare but can occur	
Arthritis	✓		Can occur
Acrodermatitis chronica atrophicans		✓	

Please note that this is an indication of what symptoms are more likely associated with the genospecies, there will always be exceptions.

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