THE NORTHERN HOSPITAL

LYME DISEASE

"Midsummer Picnic" oil on composition board, David Boyd, (1924-211).

David Boyd, grandson of the famous Australian painter Arthur Boyd, was renowned for his beautiful depictions of children playing in brilliant natural sundrenched bushland settings of the Lucky Country. We are indeed so lucky in our history, our heritage, our lifestyle, our culture, our way of life - a blessed land for our children to grow up in. We are also lucky with our bush ticks! Unlike those of the Northern Hemisphere, they do not appear carry the spirochete that causes lyme disease! (- although sadly they can carry the paralysis toxin - not so lucky there!).

LYME DISEASE

Introduction

Lyme disease is a tick-borne zoonosis caused by the spirochaete bacterium, ***Borrelia burgdorferi*.**

Lyme disease is one of the most frequently reported human tick-borne infections worldwide.

It has been "reported" from every continent (except Antarctica) and "Lyme Disease Associations" exist in Europe, America and Australia, however, current expert medical opinion casts **significant doubt** as to whether it even occurs in the southern hemisphere in general and in **Australia** in particular. [4]

There is no current convincing evidence that classic Lyme disease occurs in Australia, nor is there evidence that the causative agent, Borrelia burgdorferi, is found in Australian animals or ticks. [4]

Lyme disease, however, can be **acquired overseas** and then be diagnosed in Australia, and most people presenting with **laboratory-confirmed** Lyme disease in Australia were infected in **Europe.** [4]

Despite the lack of evidence that Lyme disease can be acquired in Australia, growing numbers of patients, their supporters, and some politicians demand diagnoses and treatment according to the protocols of the "chronic Lyme disease" school of thought.

Controversy is not only restricted to whether B. burgdorferi s.l. and a competent tick vector exist in Australia, but also whether "*chronic* Lyme disease" exists.

Antibiotic therapy for chronic "Lyme disease-like illness" can cause harm to both the individual (e.g., cannula-related intravenous sepsis) and the broader community (increased antimicrobial resistance rates).

Until there is strong evidence from well performed clinical studies that bacteria present in Australia cause a chronic debilitating illness that responds to prolonged antibiotics, treating patients with "Lyme disease-like illness" with prolonged antibiotic therapy is unjustified, and is likely to do much more harm than good.

History

This disease was first fully recognised in 1975 when a statistically improbable cluster of pediatric arthritis occurred in the region around **Lyme, Connecticut.**

Interestingly studies of the DNA taken from ticks in the Natural History Museum, London, show that the infection was present in Victorian times and so it is probably not a new illness.

Epidemiology

Lyme disease is the most frequently reported human tick-borne infection worldwide; being endemic in North America, Europe, and Asia, although significant doubt remains as to whether it occurs in the southern hemisphere in general and in Australia in particular.

The existence of lyme disease in Australia is controversial and will remain so until an organism is isolated from a local patient and fully characterised, or until a tick-borne organism can be shown to be responsible for the human infection.

If it exists in Australia it shares few of the epidemiological or clinical characteristics of North American or European patterns of lyme disease. [1]

Pathology

Organism

- **Borrelia burgdorferi**, a bacterial spirochete species.

In fact, four different strains of *B.burgdorferi* have been described:

- *B. burgdorferi sensu strict*
- *B. Garinii (exclusively in Europe)*
- *B. Afzelii (mainly in Europe)*
- *B. japonica.*

Each is associated with different patterns of disease, (which probably explains difference seen between European cases and North American cases) any of which can mimic other diseases.

Borrelia burgdorferi in Australia:

Despite intensive efforts, the bacteria that cause Lyme disease, Borrelia species collectively termed the Borrelia burgdorferi sensu lato (B. burgdorferi s.l.) complex, have not been cultured from any definite locally acquired cases of the disease.

Further, Australia does not appear to have a competent tick vector for these species.

Finally, bacterial DNA has not been definitively detected in patients for whom acquisition in a country where B. burgdorferi is known to be endemic could be excluded.

Pathophysiology

It is thought that the manifestations of lyme disease are caused by a combination of

- Active infection by the spirochete

- Auto-immune/ immunopathogenetic mechanisms including individual genetic predisposition.

Transmission

Lyme disease is a zoonotic tick borne disease.

It is transmitted to humans by the bite of an infected tick of the genus *Ixodes*.

The only species of ticks shown to be competent vectors of *B.burgdorferi* to humans belong to the *Ixodes persulcatus* complex, including:

- *I. scapularis* and *I. pacificus* in the United States.
- *I. ricinus* in Western Europe.
- *I. persulcatus* in Eastern Europe and Asia.

No species of this complex exist in Australia.

There is no evidence that Lyme disease is transmitted from person-to-person.

Untreated Lyme disease during pregnancy may lead to infection of the placenta and possible stillbirth.[2]

There are no reports of Lyme disease transmission from breast milk. [2]

Incubation Period

- Up to 30 days

Reservoir

- In the northern hemisphere, small placental mammals are the reservoir hosts.

Clinical Features

Around the globe, the epithet of "the great imitator" is commonly used for the clinical features of Lyme disease just as it once was for another major spirochaetal disease, prominent in previous centuries - syphilis. This is because of its wide spectrum of non-specific symptoms.

Three clinical stages are generally recognized:

Stage I, (early localized, within 2-3 weeks of tick bite):

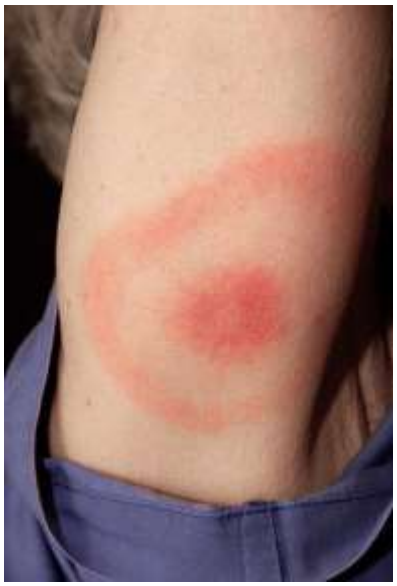
Features include:

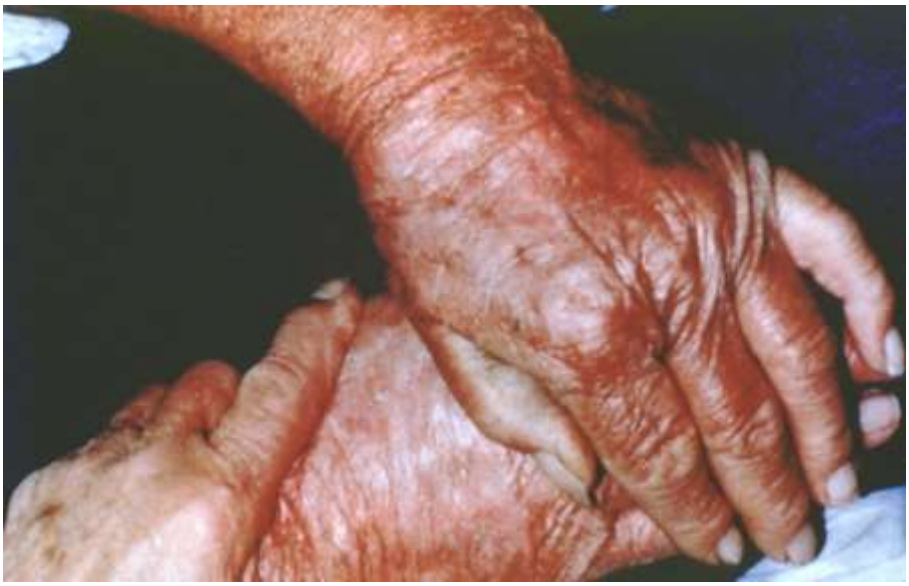
1. Non-specific "constitutional" symptoms, including:

- Fever
- Fatigue
- Malaise
- Headaches
- Myalgia
- Arthralgia (but not true arthritis)

2. Lymphadenopathy

3. Dermatological:





Left: Erythema migrans lesion on the inner upper arm of a woman with stage I lyme disease.

Right: Acrodermatitis chronica atrophicans. This is found almost exclusively in European patients and comprises an early inflammatory phase and a later atrophic phase. As the term suggests, the lesion occurs acrally and ultimately results in skin described as being like cigarette paper. (from Lyme Disease Foundation, Hartford, Conn).

A characteristic skin lesion, **erythema migrans**, appears 3-30 days after the bite of an infected tick, usually at the site of inoculation.

The lesion begins as a red maculo-papular area generally greater than 5 cm in diameter. It is not usually painful. It may grow to reach over 50 cm in diameter, later with central clearing with a well defined, circinate or “bulls-eye” centre.

Multiple lesions at different stages of evolution may be present.

Allergic reactions, associated with tick bites, may be confused with early **erythema migrans** , but these occur within a few hours of the bite and resolve within a few days.

In North America **erythema migrans** occurs in up to 80% of serologically confirmed cases of lyme disease.

Note that some cases can be subclinical, with patients naturally clearing the infection, (but becoming seropositive).

Stage II: (early disseminated, weeks to months after the tick bite):

Lesions resembling those of secondary syphilis occur, though a direct causative association is often not clear.

The following may be seen:

- Myocarditis
- Chronic meningitis
- Mononeuritis (in particular Bell's palsy)
- Conjunctivitis.
- Arthralgias and myalgias remain prominent.

Stage III, (late or chronic disseminated stage, months to years after the tick bite):

The most characteristic features seen in North American cases include:

- Erosive arthritis of large joints, particularly the knees.

The most characteristic features seen in European cases include:

- A chronic skin manifestation known as **acrodermatitis chronica atrophicans**

A host of other non-specific symptoms are frequently attributed by the lay public to stage III chronic lyme disease, but attributing direct causation for many of these symptoms is controversial and problematic in many cases.

*Controversy regarding chronic Lyme Disease***:**

Controversy is not restricted to whether B. burgdorferi s.l. and a competent tick vector exist in Australia. It also exists over whether chronic Lyme disease exists here.

This concept does not require the aetiological agent to be metabolically active beyond maintaining a resting metabolism; it need only be present in the patient and viable.

Further, the term “chronic Lyme disease” is not consistently defined: it has been applied to patients who present with active, previously untreated B. burgdorferi s.l. infections, to those who have persistent symptoms after being treated for Lyme borreliosis, to people who have had Lyme borreliosis in the past but whose current illness is unrelated to that infection, and to patients without any history of borreliosis.

In Australia, substantial numbers of patients without evidence of current or past B. burgdorferi s.l. infection have been labelled with “chronic Lyme” or “Lyme-like disease”, often after bites by Australian ticks.

However, even in countries where classic Lyme disease is endemic, the mainstream medical position is that persistence of infection has not been demonstrated in vivo; lingering, non-specific symptoms appear to be post-infectious sequelae unrelated to ongoing active infection.

Internationally, the concept of chronic Lyme disease polarises opinion. In the United States, the key protagonists in the debate are the Infectious Diseases Society of America (IDSA), an association of physicians and medical scientists, and the public advocacy group, the International Lyme and Associated Diseases Society (ILADS).

Consistent with its model of persistent infection, ILADS and practitioners who share its views advocate long term treatment with oral antibiotics and sometimes prolonged use of intravenous antibacterial agents and associated complementary therapies, such as probiotics and natural and alternative therapies, for managing

Investigations

With the possible exceptions of typical erythema migrans and acrodermatitis chronica atrophicans associated with appropriate exposure, clinical features alone are insufficient for diagnosis of lyme disease and laboratory tests are required for confirmation.

Biopsy:

Isolation of the causative organism can be achieved from a punch biopsy taken at the edge of an **erythema migrans** lesion.

This will be positive in up to 80% of cases however it may take up to 8 weeks before spirochaetes can be detected.

PCR testing:

Polymerase chain reaction (PCR) testing of the biopsy specimen is more sensitive and results may be available within 24 hours.

Serology:

Laboratory diagnosis of late lyme disease (Stage II and III) is less reliable and depends on various serological tests including:

- Indirect fluorescence antibody test (IFAT)

- Enzyme linked immunosorbent assay (ELISA)
- Western immunoblot (WB)

False positive results may occur due to cross reactions with other bacteria, especially other spirochaetes, viruses and in unrelated syndromes such as autoimmune diseases.

IFAT and ELISA are used as *screening tests* but there has been little standardisation of methods.

Any borderline or positive results should be confirmed by WB testing.

If a patient both receives a confirmed reactive antibody result from an appropriately accredited medical testing laboratory and presents with symptoms consistent with the relevant disease, the predictive value of the positive test result increases. However, these conditions do not appear to have been met for any patient diagnosed with possible Lyme disease acquired in Australia. [4]

See also Appendix 1 below.

Management

Early lyme disease (i.e. stage I), can be treated with antibiotics and will usually result in complete recovery.

Expert Infectious Diseases opinion should be sort regarding the best treatment.

Commonly used agents include:

- A two week course of oral **doxycycline** or **amoxycillin** for Stage I
- A third generation cephalosporin for Stage II

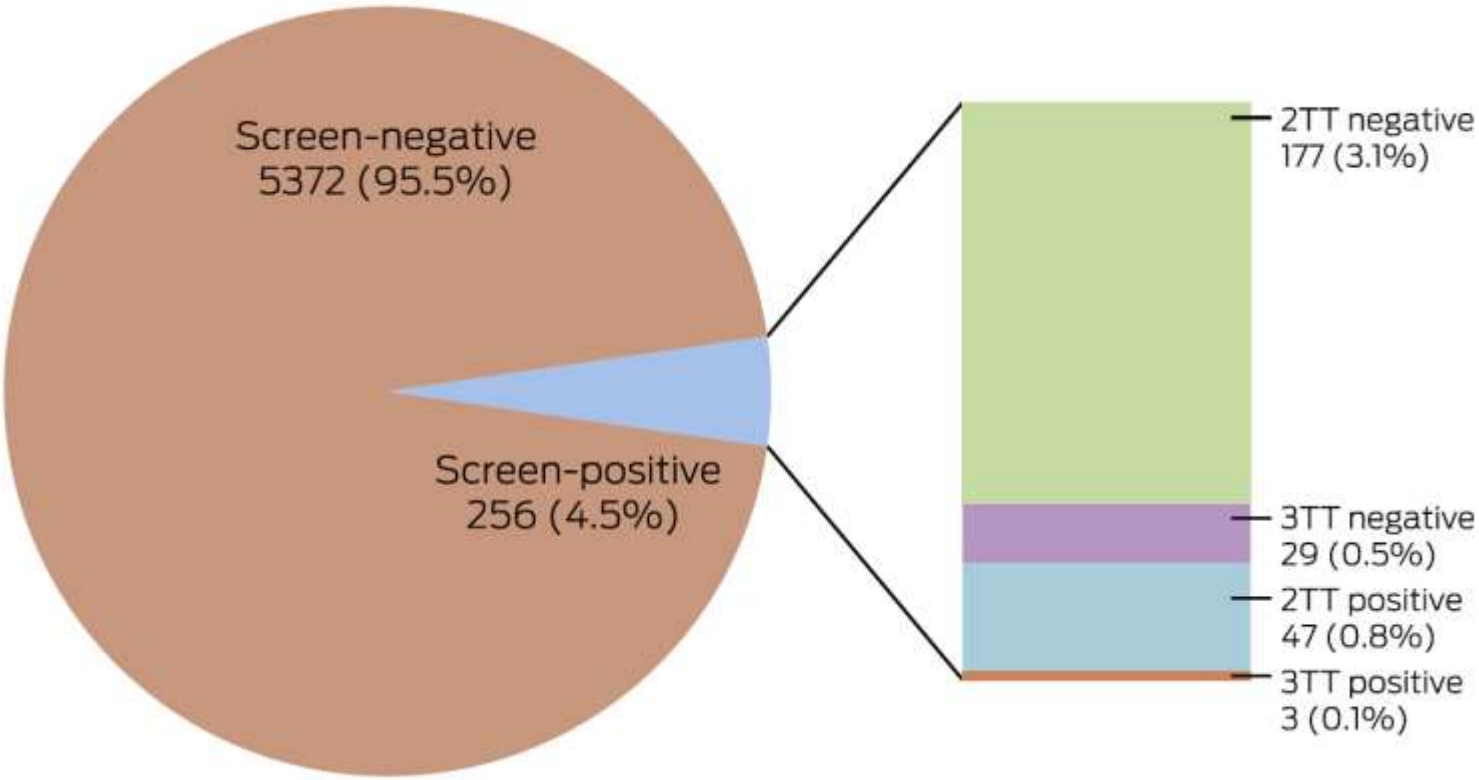
Antibiotic treatment of so-called "chronic Lyme disease" is extremely controversial.

Further research, using next generation sequencing and metagenomics, may in the future identify links between specific tick-borne pathogens and patients who present with a constellation of chronic, non-specific symptoms, but it is only after such a link has been definitely established that effective, evidence-based management protocols can be safely developed.

Until there is strong evidence from well performed clinical studies that bacteria present in Australia cause a chronic debilitating illness that responds to prolonged antibiotics, treating patients with "chronic lyme disease" or "Lyme disease-like illness" with prolonged antibiotic therapy is unjustified, and is likely to do much more harm than good, due to antibiotic side effects and the selection of super-resistant microorganisms.

Appendix 1

Lyme Disease testing in Australia:



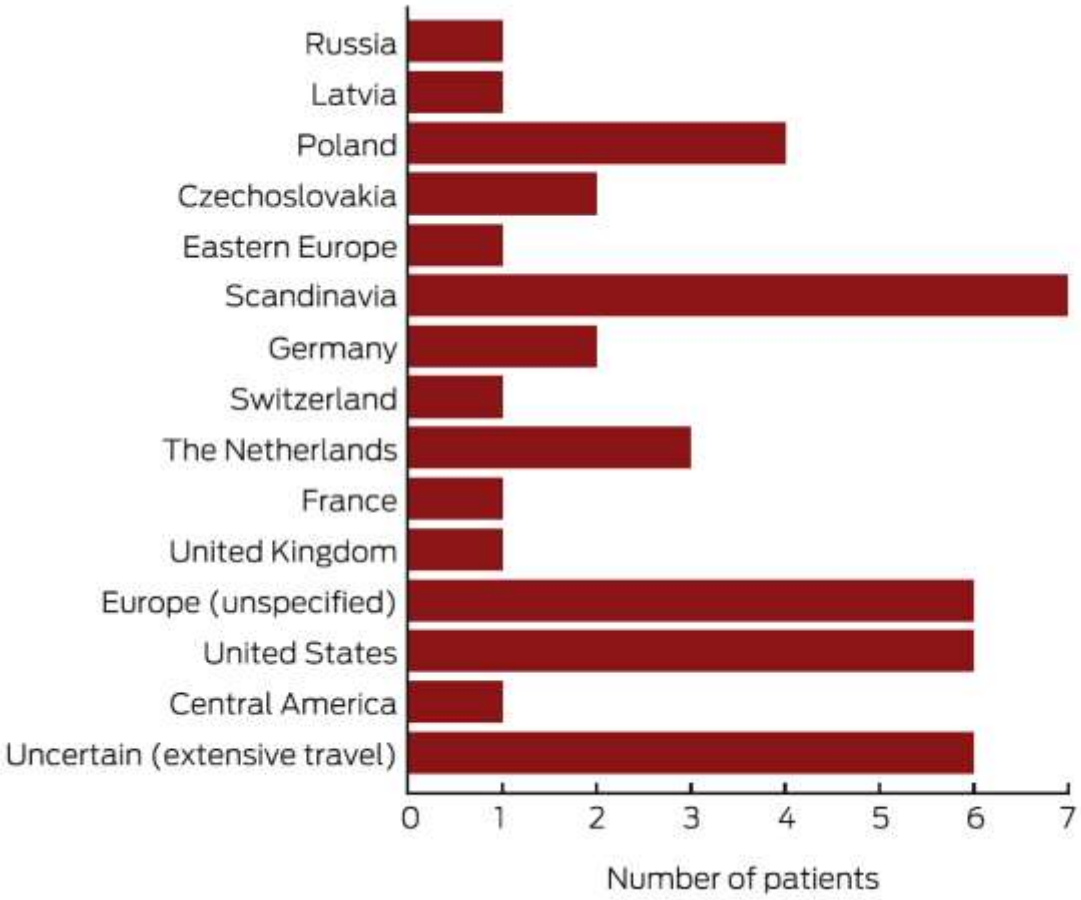
The results of Lyme disease antibody test requests, Australia, September 2014 - July 2016

In two-tier testing (2TT), the screening assay used was the recombinant VlsE-based Liaison chemiluminescence immunoassay for Borrelia burgdorferi (IgG) (DiaSorin); the second tier test employed was the anti-Borrelia burgdorferi IgG Euroline-RN-AT immunoblot system (Euroimmun).

For the second series of immunoblot tests (3TT; performed on a subset of mostly low pre-test probability specimens), an in-house IgG western immunoblot for B. Burgdorferi and B. afzelii, or the MarDx IgG EU Lyme (B. afzelii, B. garinii) þ VlsE western blot system (Trinity Biotech) was used. 3TT was performed at Pathology West e ICPMR Westmead, Sydney. [3]

Appendix 2

Travel History in Australian Patients testing positive for Lyme Disease:



The travel history for 43 patients with positive serological test results for Lyme disease (3-tier testing) [3]

“A Small Saint in Search of Solitude”, oil on linen, David Boyd.

References

1. Lyme Disease: The Department of Medical Entomology, University of Sydney and Westmead Hospital, Australia.

    - http://medent.usyd.edu.au

2. Lyme Disease in CDC Website, 19 August, 2016

3. Peter J Collignon et al. Does Lyme disease exist in Australia? MJA 205 (9) 7 November 2016.

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Reviewed November 2016.