DSCATT Clinical Pathway

DRAFT FOR OCTOBER CONSULTATION

On behalf of the Australian Government Department of Health

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ALLEN+CLARKE

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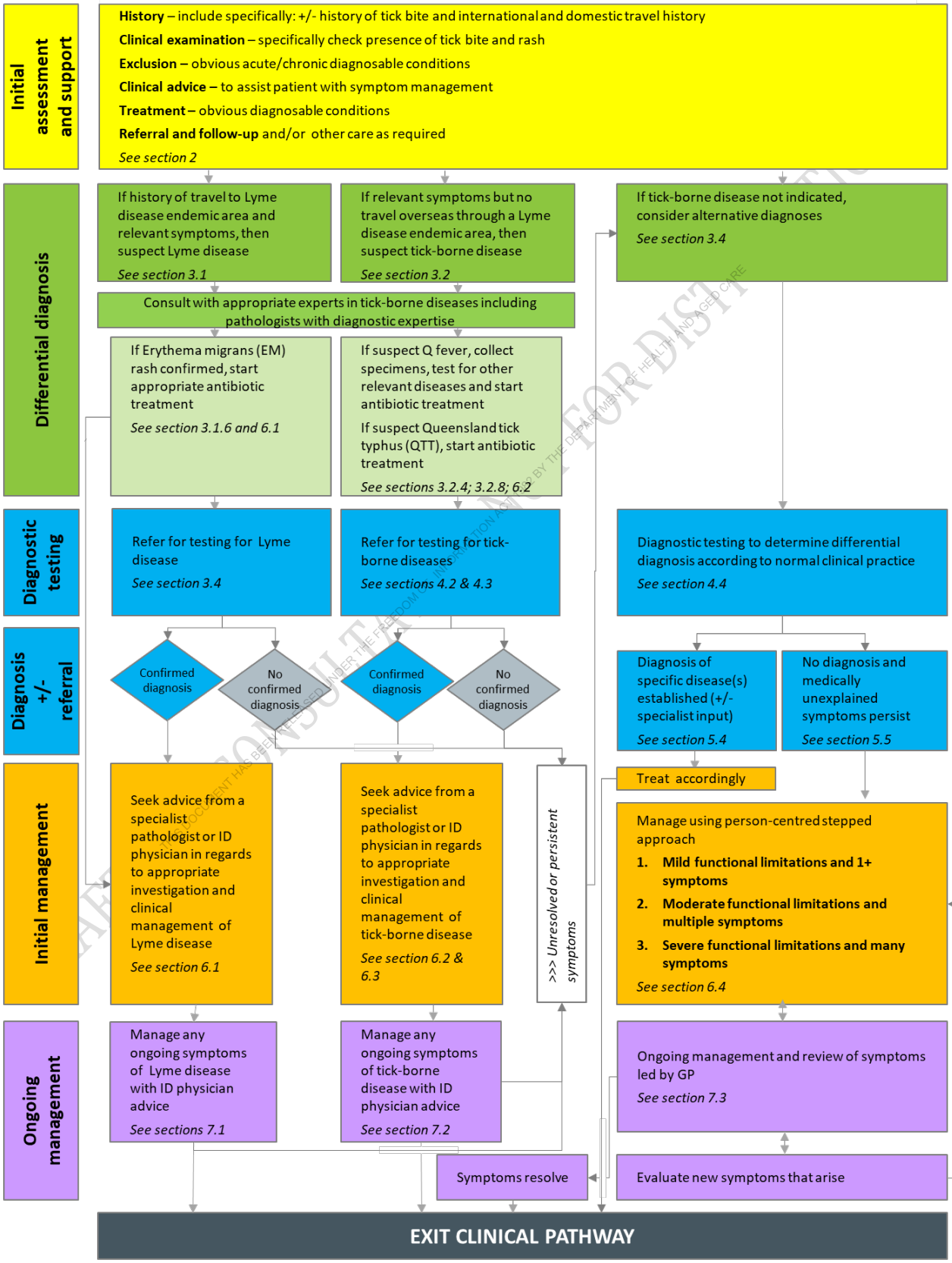
Draft DSCATT Clinical Pathway

(Note: Patients may be on multiple parts of the pathway simultaneously)

Target population: Patients of all ages presenting at primary care with new onset (e.g. fever, rash) or unresolved debilitating symptoms, +/- history of tick bites



SUMMARY INFORMATION

The Debilitating Symptom Complexes Attributed to Ticks (DSCATT) Draft Clinical Pathway has been developed to support decision-making on differential diagnosis and referral pathways for patients presenting with either new onset or unresolved debilitating symptoms with or without a history of tick bites and that cannot be attributed to another condition (acute or chronic).

Initial Assessment

- Follow usual clinical assessment practice including a travel history.
- Tick bite diagnoses are challenging as clinical features can be similar to many other diseases (infectious and non-infectious). Consult with appropriate experts in vector-borne diseases including specialist pathologists with diagnostic experience and infectious disease (ID) physicians for treatment of diagnosed vector-borne diseases.

Lyme disease (only patients who have travelled overseas to Lyme endemic areas)

- In patients presenting with a history of travel to Lyme disease endemic areas (Europe, North America, Asia), exposure to tick bites and with relevant clinical symptoms, suspect Lyme disease.
- *Do NOT test for Lyme disease if patients have NOT travelled to Lyme endemic areas* as tests may show false positives, with a risk of missing an alternative diagnosis and providing inappropriate treatment. It is important to ensure that conditions such as tumours, multiple sclerosis and motor neurone disease are not misdiagnosed as Lyme disease.
- For patients presenting with a bull's-eye rash (Erythema migrans) and a relevant travel history, seek advice from an infectious diseases specialist in regards to the appropriate investigations and treatments that are clinically relevant to the patient's presentation and commence antibiotic therapy.
- Diagnostic testing for Lyme disease should only be initiated following advice from appropriate experts such as a consultant physician practising in his or her speciality of infectious disease or a specialist pathologist in his or her speciality of microbiology and should only be undertaken in Australia in a pathology laboratory accredited by National Association of Testing Authorities (NATA) or Royal College of Physicians (RCPA) to conduct such testing.
- If there is no Erythema migrans (EM), a course of antibiotic treatment for Lyme disease should only be initiated based on the expert advice of either a consultant physician practising in his or her speciality of infectious disease or a specialist pathologist in his or her speciality of microbiology. This advice will be based upon results of confirmatory testing conducted in a NATA/RCPA accredited laboratory and/or other clinical findings relevant to informing a treatment decision.
- For patients with ongoing symptoms after one course of antibiotics, only one additional course of antibiotics may be recommended as there is no evidence of benefit of longer courses. An additional course of antibiotics will be determined on case by case basis. Full resolution of symptoms may take some time but does not require further antibiotics.
- Therapeutic modalities not recommended for treatment of patients with any manifestation of Lyme disease include combinations of antimicrobials, long-term antibiotic therapy, hyperbaric oxygen, fever therapy, intravenous immunoglobulin, ozone, cholestyramine, energy and radiation-based therapies, vitamins and nutritional managements, magnesium and bismuth injections, chelation and heavy metal therapies, stem cell transplants.

Australian and international vector borne disease

- In patients who have not travelled overseas to a Lyme endemic areas, AND who have or may have been recently bitten by a vector, such as a mosquito or tick, AND present with acute onset, suspect Australian vector-borne disease and seek expert advice as per above.

  Also check whether the history of travel aligns with either epidemic or endemic areas for other vector borne diseases not just ticks.

Mosquito borne disease

- While some mosquito borne diseases are locally acquired in Australia, others are imported to Australia when people acquire the disease travelling overseas and return unwell.

- Some types of mosquitoes can transmit viruses such as Ross River and Barmah Forest in most parts of Australia and, rarely, the virus that causes Murray Valley encephalitis. Some parts of northern Queensland have a type of mosquito (Aedes aegypti) that are capable of transmitting dengue fever, chikungunya and zika infections. Dengue outbreaks have known to occur from time to time in Queensland while chikungunya and zika are mainly seen in imported cases.
- Mosquito borne diseases are notifiable to public health authorities. If clinically suspected, seek appropriate expert advice where necessary on both appropriate sampling and testing that should be requested to confirm diagnosis.
- Overseas travelers may be at risk of mosquito-borne diseases such as malaria, dengue, yellow fever, chikungunya, or zika. While vaccines are available for some diseases (e.g. yellow fever and Japanese encephalitis) and chemoprophylaxis medicine can help prevent malaria, all travelers should also use repellents and other general protective measures to avoid mosquito bites. The same general protection measures also apply to locally acquired mosquito borne disease.

Tick borne disease known to be acquired in Australia

- Diagnosis of tick-borne disease known to exist in Australia is challenging. Symptoms may overlap with other infectious diseases including those that are transmitted by non-tick vectors as well as a number of chronic diseases. Seek further expert opinion as necessary depending upon the nature of the patient's clinical presentation. Apart from the occasional local bacterial infection at the tick bite site (eschar) the only two systemic infections that are definitely known to be transmitted by tick bites in Australia are **Rickettsial infections** from infection with *Rickettsia* spp. (Queensland tick typhus, Flinders Island spotted fever and Australian spotted fever) and **Q fever** (*Coxiella burnetii*).
- ***Queensland tick typhus (QTT)***, Early recognition and treatment is important. ***see Therapeutic Guidelines antibiotic for treatment***.
- ***Flinders Island Spotted Fever (FISF) and Australian Spotted Fever (ASF) see Therapeutic Guidelines antibiotic for treatment.***
- ***Q fever*** *(Coxiella burnetii)* ***see Therapeutic Guidelines antibiotic for treatment***. Q fever is a nationally notifiable disease. Q fever is acquired via various modes of transmission, a minority of which is tick borne.

Tick borne disease not acquired in Australia

- ***Tick-borne encephalitis (TBE)*** is a human viral infectious disease, transmitted by the bite of infected ticks in woodland habitats, and involves the central nervous system. It occurs in many parts of Europe and Asia. It can also be transmitted by the consumption of unpasteurised/raw milk and dairy products.

Tick removal and bite prevention

- If a tick has embedded in the patient's skin and remains in situ, enquire whether the patient suffers from allergies to ticks before attempting to remove the tick. Removing a tick must occur in a medical facility with capacity to initiate advanced life support in the event of anaphylaxis.
- The best way to prevent tick bites is to avoid tick-infested areas. If this is not possible patients should be advised to wear appropriate clothing such as long sleeve shirt, long pants tucked into socks and light coloured clothing to make it easier to see ticks before they attach to skin.
- Insecticides containing either diethyl-meta-toluamide (DEET) or picaridin should be applied to the skin prior to entering a tick infested area. Permethrin treated clothing is considered the most effected means of tick bite prevention.

Management of patients who have persistent symptoms or remain undiagnosed

- If the symptoms are medically unexplained, general practice should treat and manage symptoms according to common practice and provide person-centred stepped care. Stepped care includes:
  - developing an individualised, time contingent, care plan
  - actively managing symptoms to improve the functioning of the patient in accordance with evidence-based guidelines
  - offering a variety of support options for people with different levels and types of need, from low intensity to high intensity
  - providing clear pathways between these care options as individuals' needs change
  - intensifying stepped care as required by referring to relevant specialists
  - providing regular follow-up and exploring symptoms if recovery stagnates
  - reviewing new symptoms for providing a piece of information that may lead to diagnosis, or for indications of a new disease process

Practice harm minimisation by avoiding repeated diagnostic testing, use of non-accredited laboratories for diagnostic testing and use of unconventional diagnostic techniques, unnecessary referrals and interventions, and treatments with known harm and no benefit.

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GLOSSARY

ALLI	Australian Lyme-like Illness
CBT	Cognitive behavioural therapy
CDC	Centers for Disease Control and Prevention
CDNA	Communicable Diseases Network Australia
DEET	Diethyl-meta-toluamide
DSCATT	Debilitating Symptom Complexes Attributed to Ticks
ELISA	Enzyme-linked immunosorbent assay
EM	Erythema Migrans. Bull's Eye Rash
FSIF	Flinders Island Spotted Fever
GI	Glycaemic Index
GP	General Practitioner
ID	Infectious Disease
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IDSA	Infectious Disease Society of America
MBS	Medical Benefits Schedule
MUS	Medically Unexplained Symptoms
NATA	National Association of Testing Authorities, Australia
NICE	National Institute of Health and Care Excellence (UK)
NHMRC	National Health and Medical Research Council
NRL	National Serology Reference Laboratory
PCR	Polymerised Chain Reaction
RACGP	Royal Australian College of General Practitioners
RCPA	Royal College of Pathologists of Australasia
TBE	Tick-borne encephalitis
TGA	Therapeutic Goods Administration
QFS	Q Fever Fatigue Syndrome
QTT	Queensland Tick Typhus

1. INTRODUCTION

1.1. Purpose of the Clinical Pathway

This evidence-based Clinical Pathway has been developed to support decision-making on differential diagnosis and referral pathways for patients presenting with either new onset or unresolved debilitating symptoms with or without a history of tick bites and that cannot be attributed to another condition (acute or chronic). It has also been designed specifically for the Australian health care context in order for it to be generally accepted by the Australian medical and other health professions and patient groups as a part of their clinical management.

1.2. Debilitating symptom complexes attributed to ticks (DSCATT)

Debilitating symptom complexes attributed to ticks (DSCATT) is the term used by the Australian Government to describe the group of Australian patients suffering from the symptoms of a chronic debilitating illness, which many associate with a tick bite[1], to appropriately acknowledge this patient group and the multifaceted illness they are experiencing, and acknowledge their illness is poorly understood. The Australian Government acknowledges that many of these patients experiencing debilitating symptom complexes are living in turmoil. With the causes of DSCATT as yet unknown, the Australian Government urges patients and health professionals to keep an open mind about the cause of a patient's symptoms.

DSCATT was also proposed as a name to move away from the stigma and controversy associated with the terms previously used to describe this patient group such as "*Lyme disease-like Illness*" and "*Chronic Lyme Disease*"[2].

DSCATT is not clearly defined and is not formally reported. It has no diagnostic criteria, known cause or causes, no treatment and these symptoms may be the end point for several different disease processes. The symptom complexes to which the name DSCATT has been given incorporates a wide range of nonspecific symptoms. Some people may have a diagnosis that has not yet been identified that explains these symptoms while others may have a cluster of medically unexplained symptoms that require management.

People with medically unexplained symptoms (MUS) may obtain a diagnosis over time as symptoms develop and guide to the origin of the illness. Others may find that symptoms resolve over time, without ever identifying a cause. All people with medically unexplained symptoms, (including those given the title DSCATT) can be assisted to have an improved quality of life with good care in a partnership between patient and the health care team.

There are no peer-reviewed published epidemiological or clinical studies about patients experiencing DSCATT. The only relevant information available is self-reported and anecdotal. Patients have told of the symptoms they have experienced and attribute to DSCATT to the Senate

[1] Department of Health (June 2018)
[2] Department of Health (June 2018)

Community Affairs References Committee[3,4], DSCATT Patient Forum[5] and Think Tank[6]. The most common symptoms described by patients with DSCATT to the Senate Forum were: fatigue (62.6%); disordered thinking (51.9%); sensory disturbance (46.1%); arthralgia (45.6%;) headache (44.5%); followed by myalgia; rash; mood disturbance; visual disturbance; dizziness; pain; fever; nausea; palpitations; insomnia; seizures; diarrhoea; tremor; and personality change[7]. Patients reported having experienced symptoms for a median of 10 years and had seen a median of 13 doctors for diagnosis and treatment of their illness. An analysis of the Senate submissions noted the unquestionable real and debilitating physical and social harm from illness reported in the submissions. Of relevance to the attribution of symptoms to ticks, over half of the submissions analysed did not comment on tick bite but of those that did, a majority (89.5%) reported a positive history. The author's conclusion suggested that patients who identified as having DSCATT displayed a symptomology similar to 'medically unexplained physical symptoms' syndromes, and also experience social and financial harms and are at risk of nosocomial harms. They may also have sought alternative and potentially non-evidence-based diagnoses and treatments.[8]

Similarly, multiple symptoms and signs being attributed to DSCATT were identified by stakeholders who attended the Think Tank in May 2019, with neurological symptoms (including brain fog, cognitive dysfunction, memory loss, fine motor impairment and reduced verbal fluency) and chronic fatigue being the most commonly identified symptoms and signs.[9]

1.3. Consideration of tick-borne diseases in the differential diagnosis

Acknowledging the attribution to ticks in the term DSCATT, this Clinical Pathway includes the consideration of tick-borne diseases in the differential diagnosis (overseas-acquired Lyme disease and known Australian tick-borne diseases) and considerations and referral pathways for patients for whom a diagnosis for their symptoms may not be established.

1.4. Management of patients with persistent symptoms or who remain undiagnosed

The Clinical Pathway acknowledges that because of the imprecise nature of the symptom complexes some patients will remain undiagnosed. Therefore evidence-based ways to manage ongoing symptoms through a comprehensive patient-centred care plan has been included for patients for whom there is no diagnosis and who are considered to have medically unexplained symptoms or 'undifferentiated illness'.

Where there is no diagnosis, and the patient is experiencing symptoms that are medically unexplained, it is especially important to ensure that patient or person-centred care is provided that validates, addresses and manages their symptoms as well as possible.

[3] The Senate Community Affairs References Committee (May 2016)
[4] The Senate Community Affairs References Committee (November 2016)
[5] Department of Health Patient Group Forum (27 July 2018)
[6] DSCATT Think Tank Summary Report (May 2019)
[7] Brown (2018)
[8] Brown (2018)
[9] DSCATT Think Tank Summary Report (May 2019)

2. INITIAL ASSESSMENT AND SUPPORT

The initial assessment and support for a patient who presents at primary care with new onset of fever or rash or persistent debilitating symptoms (with or without a history of tick bites) should follow usual clinical practice. The Clinical Pathway is to assist general practitioners (GPs) with the diagnosis and management of patients who are assessed to be clinically stable.

2.1.1. Follow usual clinical assessment practice including a travel history

Initial assessment and support should include:

- in the clinical examination of an acute case, specifically check for the presence of tick bite or other rashes;
- from the history and examination, exclude obvious acute illnesses or chronic diagnosable conditions;
- treat obvious diagnosable conditions;
- provide clinical advice to assist patient with symptom management while investigating any differential diagnoses; and
- arrange referral and follow-up and/or other care as required.

The inclusion of a travel history as part of the clinical history is important, as the organism that causes Lyme disease has not yet been identified in Australia, but is endemic in parts of the USA, Europe and Asia. Not all persons with Lyme disease recall having had a tick bite or notice a tick bite, thus a history of travel or exposure in a known endemic area for Lyme disease should be sought from possible cases[10]. If a person presents with symptoms that suggest the possibility of Lyme disease, explore how long the person has had the symptoms and their history of possible tick exposure, and ask about activities that might have exposed them to ticks, and travel to areas where Lyme disease is known to be highly prevalent[11].

In patients who have not travelled internationally and present with symptoms suspicious for an Australian tick-borne disease, knowledge of where the patient has travelled in Australia will assist with differential diagnosis. Mosquito-borne diseases may present in the acute phase very similarly and a person who is at risk of tick bites is also likely to be at risk of mosquito bites which can appear very similar if the tick is not actually stuck on the skin, particularly if the wound is inflamed and scratched. It is recommended that medical practitioners keep an open mind when patients speak of symptoms associated with tick bites as while the patient may have other underlying medical issues brought to light at the time of the tick bite, a considered investigation of the whole clinical history is indicated[12].

2.1.2. Consult with appropriate experts in vector-borne disease

Tick bite diagnoses are challenging as clinical features can be similar to many other diseases (infectious and non-infectious). Consult with appropriate experts in vector-borne diseases

[10] RCPA (May 2019)
[11] NICE (April 2018a)
[12] Graves and Stenos (2017)

including specialist pathologists with diagnostic experience and infectious disease (ID) physicians for treatment of diagnosed vector-borne diseases.

3. DIFFERENTIAL DIAGNOSIS

3.1. Lyme disease

In Australia, Lyme disease should be considered in patients presenting with a travel history to Lyme-endemic areas along with supporting symptoms and/or a known tick bite[13].

While there are good overseas guidelines on Lyme disease, they may not all be applicable to the Australian context. If Lyme disease is suspected, consult with appropriate experts such as a consultant physician practising in his or her speciality of infectious disease or a specialist pathologist in his or her specialty of microbiology. The recommendation to seek advice from an ID specialist in Australia, where cases of overseas acquired Lyme disease are very rare, is important. The difficulty in diagnosing Lyme disease, even in Lyme disease endemic areas, was highlighted in a systematic review that found that clinicians find it challenging to diagnose accurately due to the wide variation in symptom; the infrequency with which they see the disease in practice; their level of confidence about being able to diagnose correctly; the ambiguity they experience about diagnostic tools; and their beliefs and behaviour relating to atypical or recurring symptoms[14].

Areas where Lyme disease is endemic internationally, clinical presentation of Lyme disease and special recommendations when considering a differential diagnosis of Lyme disease in a patient in Australia are covered in sections 3.1.1 to 3.1.5.

Follow usual clinical practice to manage symptoms, such as analgesia for headaches or muscle pain, in patients being assessed for Lyme disease[15].

3.1.1. Transmission and geographical distribution of Lyme disease

Lyme disease is endemic in parts of the USA, Europe and Asia. A person visiting a Lyme-endemic area may become infected with *Borrelia burgdorferi* sensu lato through a tick bite and subsequently develop Lyme disease. Overseas travellers to Lyme-endemic areas may return to their home country before becoming symptomatic and/or being diagnosed.

Lyme disease is an infectious disease that can be transmitted to humans who are bitten by a tick carrying different species of *Borrelia* bacteria (spirochaetes) collectively known as *Borrelia burgdorferi* sensu lato[16,17,18,19]. In Lyme disease endemic areas, the risk of *Borrelia* infection after the bite of an infected tick is low at only 1% and 3% in the United States and 3-12% in Europe[20]. The duration of tick attachment is one of the most important predictors of subsequent Lyme

[13] Department of Health (June 2018)
[14] Brunton et al. (2017)
[15] NICE (April 2018a)
[16] Department of Health (June 2018)
[17] RCPA (May 2019)
[18] McKenzie (2013)
[19] NICE guideline Lyme disease. (April 2018)
[20] Borchers et al. (2015)

disease with infection more likely the longer a tick is attached to the skin[21,22,23,24]. The incubation period is typically seven to fourteen days, but may be shorter, or longer (up to 30 days)[25].

More than 18 spirochaete species comprise the *B. burgdorferi s.l.* complex. Four species are found only in North America, eleven species occur in and are restricted to Eurasia and three species occur in North America and Europe[26].

The main species within this group include:

- *Borrelia burgdorferi* sensu stricto (North America, Europe);
- *Borrelia afzelii* (in Europe, China); and
- *Borrelia garinii* (in Europe, Asia)[27,28]

Of the three main genospecies *B. garinii* and *B. afzelii* are antigenically distinct from *B. burgdorferi* s.s. which may account for the variation in clinical presentation in different geographic regions[29].

Less common species known to cause Lyme borreliosis include *B. bavariensis* (in Europe), *B. bissetiae* (United States, Europe), *B. lusitaniae* (Europe), *B. mayonii* (in mid-west USA), *B. spielmanii* (Europe), *B. valaisiana* (Europe, Asia)[30].

Lyme disease is found in high rates in endemic areas, mainly the north east of the USA, some areas of Europe including the UK and some parts of Asia[31]. Almost all confirmed cases of Lyme disease have occurred in the Northern Hemisphere[32]. The majority of cases come from the United States and Europe (including the European part of Russia), with far fewer cases from Asia and some from North Africa[33].

In the **United States**, the Northeast, the mid-Atlantic region and the upper Midwest are the prime areas of endemicity and ten states (Connecticut, Delaware, Massachusetts, Maryland, Minnesota, New Jersey, New York, Pennsylvania, Rhode Island and Wisconsin) account for ≥93 percent of annual cases[34].

In most of **Europe** while Lyme disease is not a reportable disease and available data are less reliable, Lyme disease is highly endemic in much of Europe. The highest incidence is reported from southern Sweden, Lithuania, Germany, Austria, and Slovenia with the total number of annual cases in Europe estimated to be about three-fold higher than the number of cases reported to the Center for Disease Control and Prevention (CDC)[35]. In the United Kingdom, infected ticks are

[21] NICE (April 2018a)
[22] McKenzie (2013)
[23] Borchers et al. (2015)
[24] Lantos et al. (2019)
[25] McKenzie (2013)
[26] McKenzie (2013)
[27] McKenzie (2013)
[28] RCPA (May 2019)
[29] McKenzie (2013)
[30] RCPA (May 2019)
[31] Department of Health (2018)
[32] Borchers et al. (2015)
[33] Borchers et al. (2015)
[34] Borchers et al. (2019)
[35] Borchers et al. (2015)

found throughout the UK and Ireland, with particularly high risk areas being the South of England and the Scottish highlands[36].

Transmission in pregnancy, sexual contact or blood products

An evidence-based review of person-to-person transmission of Lyme disease to inform the 2018 NICE Lyme disease guideline acknowledged that mother-to-baby transmission of Lyme disease is possible in theory. However, while there was an absence of evidence, the risk appears to be very low[37]. NICE also found no evidence for transmission of Lyme disease through sexual contact or blood products[38].

3.1.2. Clinical presentation of Lyme disease

Many people may not notice or remember a tick bite. Infection with *B. burgdorferi s.l.* can sometimes go unremarked, with mild symptoms that are ignored by the person. When symptoms occur, this is called Lyme disease.

A tick bite can be followed by an 'erythema migrans' rash (EM), a circular target-like rash which is considered pathognomonic for Lyme disease but can sometimes be mistaken for cellulitis or ringworm, delaying effective treatment. While the prevalence of EM is seen in about 70 percent of the cases reported to the CDC, ≥90 percent in cohorts of paediatric and adult US patients and in 70-95 percent in European epidemiological studies, central clearing of EM is seen only in 19 percent of US patients compared to almost 80 percent of European patients[39], thus illustrating the variation in clinical manifestation according to where the infection was acquired and, therefore the need to take a travel history.

If there is no EM rash or it is unnoticed, diagnosis can be difficult as the same symptoms may be caused by many other conditions as well as Lyme disease[40].

Lyme disease is customarily divided into three stages, with clinical manifestations varying in their occurrence and incidence depending on the infecting species and whether the infection was acquired in Eurasia or North America[41]. Approximately 4-8 percent of patients develop cardiac findings, 11 percent develop neurologic findings and 40–60 percent of patients manifest arthritis[42], although surveillance data over the past 15 years documents a much lower annual incidence of 30 percent for Lyme arthritis in patients with untreated EM[43] .

[36] NICE (April 2018a)
[37] NICE (April 2018b).
[38] NICE (April 2018b).
[39] Borchers et al. (2015)
[40] NICE (April 2018a)
[41] RCPA (May 2019)
[42] Borchers et al. (2015)
[43] Lantos et al. (2019)

Table 1: Stages of Lyme disease in patients who have travelled to Lyme disease endemic countries

Early stage (stage I)

• Constitutional (flu-like) signs and symptoms including headache, myalgia, arthralgia and fever may be present.[44]
• EM (usually around 7-14 days post-infected tick bite) either as a single expanding area, or a central spot surrounded by clear skin that is in turn encircled by an expanding red rash ('bull's-eye') which is centred on the tick bite is the characteristic sign of early infection in ~80% of patients.[45]
• A rash, which is not EM, can develop as a reaction to a tick bite.[46] This rash
  ○ usually develops and recedes during 48 hours from the time of the tick bite
  ○ is more likely than EM to be hot, itchy or painful, and
  ○ may be caused by an inflammatory reaction, or infection with a common skin pathogen.
Other common causes of rashes that can be mistaken for EM include:
• reaction to an insect bite
• cellulitis
• tinea corporis (ringworm)
• granuloma annulare
• erythema multiforme (if multiple lesions), and
• nummular eczema[47].

Early Dissemination (Stage II)
• Early haematogenous dissemination to other sites • Multiple EM lesions, (~20%) • Nervous system involvement (~15%) - headache, lymphocytic meningitis, mild neck stiffness, facial palsy • Cardiac involvement (~5%) - acute onset of high-grade atrioventricular conduction defects, myopericarditis, and • Joint involvement – a large joint oligoarthritis with brief attacks [48].
Late Dissemination (Stage III)
This stage can potentially occur after months to several years following the initial infection though the pathologic mechanism is unclear. It is hypothesised that any ongoing symptoms are more immune related which may or may not be a consequence to the initial infection. Ongoing infection is regarded a debatable diagnosis by medical profession globally. • ~60% present with rheumatologic involvement, intermittent attacks of joint swelling and pain in large joints, infiltration of mononuclear cells. • ~5% present with neuroborreliosis, peripheral neuropathy, spinal radicular pain, distal paresthesia, encephalopathy leading to subtle cognitive disturbances, intrathecal antibody production and, rarely, cerebrospinal fluid pleocytosis. • Acrodermatitis chronica atrophicans - a rare skin condition not seen in North American Lyme Disease[49].

[44] RCPA (May 2019)
[45] RCPA (May 2019)
[46] NICE (April 2018a)
[47] Public Health England.
[48] RCPA (May 2019)
[49] RCPA (May 2019)

3.1.3. Other presentations and considerations in diagnosing Lyme disease

Table 2: Other signs and symptoms of Lyme disease[50]

In a patient with a history of travel to a Lyme disease endemic area, consider the possibility of Lyme disease in a patient presenting with several of the following symptoms as Lyme disease is a **possible but uncommon cause** of fever and sweats, swollen glands, malaise, fatigue, neck pain or stiffness, migratory joint or muscle aches and pains, cognitive impairment, such as memory problems and difficulty concentrating ('brain fog'), headache and paraesthesia.
In a patient with a history of travel to a Lyme disease endemic area, consider the possibility of Lyme disease in a patient presenting with symptoms and signs relating to one or more organ symptoms (focal symptoms) as Lyme disease is a **possible but uncommon cause** of • neurological symptoms (facial palsy, or other unexplained cranial nerve palsies, meningitis, mononeuritis multiplex or other unexplained radiculopathy) or rarely encephalitis, neuropsychiatric presentations or unexplained white matter changes on brain imaging) • inflammatory arthritis affecting one or more joints that may be fluctuating and migratory • cardiac problems such as heart block or pericarditis • eye symptoms such as uveitis or keratitis, and • skin rashes such as acrodermatitis chronica atrophicans or lymphocytoma.
Do not rule out the possibility of Lyme disease in people with symptoms but no clear history of tick bite.
Do not diagnose Lyme disease in people without symptoms, even if they have had a tick bite.
Be cautious about diagnosing Lyme disease in people without a supportive history or positive serological testing because of the risk of: • Missing an alternative diagnosis • Providing inappropriate management

In children with developmental, behavioural or psychiatric disorders, there is no evidence to support a causal relationship between Lyme disease and developmental or behavioural disorders. Low probability testing is expected to produce disproportionate false positive results, potentially causing harm. However, as with many acute medical illnesses, Lyme disease could worsen behavioural or psychiatric symptoms in children who are predisposed to these[51].

[50] NICE (April 2018a)
[51] Lantos et al. (2019)

3.1.4. Situation in Australia in considering a differential diagnosis of Lyme disease

The organism that causes Lyme disease has not yet been identified in Australian ticks[52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63] nor any other vector that could transmit the disease to humans[64, 65]. It is for this reason that the Australian medical profession does not support the diagnosis of locally acquired Lyme disease in Australia[66]. While some Australians and healthcare providers believe that a form of 'chronic Lyme disease' exists, globally, 'chronic Lyme disease' is a disputed diagnosis which lacks sufficient supporting evidence [67, 68, 69, 70, 71].

3.1.5. Consult with appropriate Australian experts in infectious diseases

In a country such as Australia where Lyme disease is not endemic and is not commonly seen in clinical practice, there are additional challenges in diagnosing Lyme disease. The Royal College of Pathologists of Australasia[72] has published guidance on the diagnosis of Lyme disease specific to the Australian context. These guidance documents and the 2013 report by McKenzie[73] stress that due to the non-specific nature of many clinical signs and symptoms the diagnosis of Lyme disease in non-endemic Australia cannot reliably be made on clinical signs and symptoms alone as many other infectious and non-infectious diseases can have similar features to Lyme disease. Laboratory testing is essential. A diagnosis of Lyme disease requires:

- a careful medical history;
- a history of overseas travel to areas where Lyme disease is endemic; a patient must have been exposed to ticks however, a history of documented tick bite is not essential as many tick bites go unnoticed;
- objective clinical findings; and

[52] Chalada et al. (2016)
[53] Irwin et al. (2017)
[54] Gofton et al. (2015a)
[55] Gofton et al. (2015b)
[56] Graves and Stenos (2017)
[57] McKenzie (2013)
[58] Dehhaghi et al. (2019)
[59] Department of Health (June 2018)
[60] Greay et al. (2016)
[61] Beaman (2016)
[62] Loh et al. (2016)
[63] Collignon et al. (2016)
[64] Department of Health (2018)
[65] Graves and Stenos (2017)
[66] Department of Health (June 2018)
[67] Department of Health (June 2018)
[68] NICE (April 2018a)
[69] Wormser, Gary P., Raymond J. Dattwyler, Eugene D. Shapiro, John J. Halperin, Allen C. Steere, Mark S. Klempner, Peter J. Krause, et al. (November 1, 2006)
[70] Lantos, Paul M., William A. Charini, Gerald Medoff, Manuel H. Moro, David M. Mushatt, Jeffrey Parsonnet, John W. Sanders, and Carol J. Baker. (July 2010)
[71] Lantos et al. (2019)
[72] RCPA (May 2019)
[73] McKenzie (2013)

- appropriate *in vitro* diagnostic tests undertaken by NATA/RCPA accredited laboratories[74].

If Lyme disease is being considered, patients should be referred for Lyme disease serology to the GPs' regular Approved Pathology Practitioner (APP).

3.1.6. If EM rash is present and following appropriate expert advice, offer antibiotic treatment

For patients presenting with a bull's-eye rash (EM) and a relevant travel history, seek advice from an infectious diseases specialist in regards to the appropriate investigations and treatments that are clinically relevant to the patient's presentation and commence antibiotic therapy.

While EM will resolve without antibiotic treatment, evidence indicates that currently used antibiotic regimens will effectively prevent the development of disseminated manifestations of Lyme disease (for example, Lyme arthritis)[75].

A course of antibiotic treatment for Lyme disease should only be initiated based on the expert advice of either a consultant physician practising in his or her speciality of infectious disease or a specialist pathologist in his or her speciality of microbiology.

See section 6.1 for further detail.

3.2. Tick-borne disease known to be acquired in Australia

3.2.1. Suspect tick-borne disease if relevant symptoms but no overseas travel through a Lyme disease endemic area

In patients who have not travelled overseas to a Lyme endemic areas AND who have or may have been recently bitten by a vector, such as a mosquito or tick AND present with acute onset, suspect Australian vector-borne disease.

There are 17 human biting ticks known in Australia, but only six of these ticks are able to act as competent vectors for the transmission of pathogens to humans[76]. Apart from the occasional local bacterial infection at the tick bite site (eschar) the only two systemic infections that are definitely known to be transmitted by tick bites in Australia are Rickettsial infections from infection with *Rickettsia* spp. (QTT, FISF, ASF) and Q fever (*Coxiella burnetii*)[77,78,79] .

The species of Australian ticks known to bite humans and transmit bacterial infection are:

- the **paralysis tick** *(Ixodes holocyclus)* is endemic on the east coast of Australia and
  - causes QTT due to *R. australis*
  - causes Q fever due to *C. burnetii*
- the **common marsupial tick** *(Ixodes tasmani)*
  - causes QTT due to *R. australis*
  - causes ASF due to *R. honei* subsp*. Marmionii*

[74] RCPA (May 2019)
[75] Lantos et al. (2019)
[76] Dehhaghi et al. (2019)
[77] Dehhaghi et al. (2019)
[78] Graves and Stenos (2017)
[79] McKenzie (2013)

- the **Southern paralysis tick** *(Ixodes cornuatus)*
  - causes QTT due to *R. australis*
- the **ornate kangaroo tick** *(Amblyomma triguttum)* occurs throughout much of the central, northern and western Australia and
  - causes Q fever due to *C. burnetii*
- the **southern reptile tick** *(Bothriocroton hydrosauri)* occurs mainly in south-eastern Australia and
  - causes FISF due to *R. honei*
- the ***Haemaphysalis novoaeguinae*** (no common name)
  - causes ASF due to *R. honei* subsp*. marmionii*[80]

3.2.2. Diagnosis of tick-borne disease known to exist in Australia is challenging.

The symptoms of rickettsial infections in Australia include eschar, fatigue, fever, headache, myalgia and rash (macular, papular, vesicular) although the severity and duration of rickettsial diseases vary considerably[81]. QTT and ASF have similar core clinical manifestations with a range of other symptoms observed. Early clinical features are often non-specific, making diagnosis challenging[82]. Additionally, symptoms may overlap with other infectious diseases including those that are transmitted by non-tick vectors as well as a number of chronic diseases. Seek further expert advice from appropriate experts in vector-borne diseases as necessary.

Seek further expert opinion as necessary depending upon the nature of the patient's clinical presentation from appropriate experts in vector-borne diseases including specialist pathologists with diagnostic experience and ID physicians for diagnosis and treatment of vector-borne diseases.

3.2.3. Queensland tick typhus (QTT)

QTT is an emerging public health threat[83, 84] and an increasingly recognised important cause of community-acquired acute febrile illness in Eastern Australia[85]. Diagnosing *R. australis* infection can be challenging and in patients presenting with fever and a rash, epidemiologic data and knowledge of high-risk exposure activities can be valuable in considering QTT. A high degree of suspicion is required as the nonspecific symptoms in early QTT can lead to a delay in diagnosis[86]. Early recognition and treatment is therefore important.

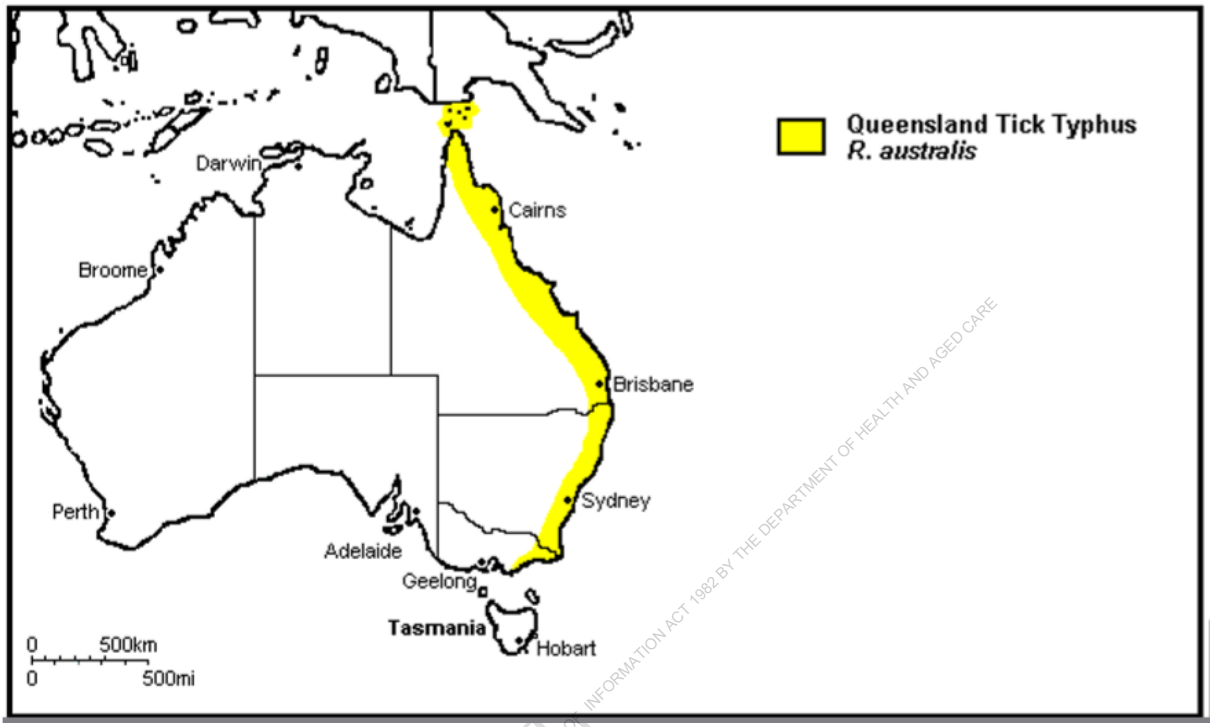
Transmission and geographic distribution

QTT is regularly seen on the east coast of Australia from the Torres Strait Islands to the south-eastern corner of Victoria, with the northern suburbs of Sydney a very common location for

[80] Graves and Stenos (2017)
[81] Dehhaghi et al. (2019)
[82] Stewart et al. (2017)
[83] Dehhaghi et al. (2019)
[84] Stewart et al. (2017)
[85] Stewart et al. (2017)
[86] Stewart et al. (2017)

transmission of this infection[87,88]. In north-eastern New South Wales, 15.4% of paralysis ticks (*Ixodes holocyclus)* were found to contain *R. australis,* suggesting a one in six risk of being infected with the rickettsia if bitten by this tick in this location[89,90]. The geographical distribution of the known human pathogen that causes QTT fever (*R. australis)* is expanding due to changes in climate and human population demographics[91].

Figure 1: Distribution of the Queensland Tick Typhus[92]



Infection by *R. australis* may occur throughout the year in immunocompetent people of all ages and ethnicities although 80% of documented cases have occurred in winter and spring (June to November) coinciding with increased tick densities in these months[93].

Clinical signs and symptoms

In symptomatic infections, QTT is often a mild condition involving fever, headache, malaise, myalgia, a rash, eschar and enlarged lymph nodes[94,95,96]. QTT may, however, be severe or fatal and may have unusual features[97]. Less common manifestations of QTT include arthralgia, splenomegaly, abdominal pain, dry cough, sore throat conjunctivitis and photophobia[98]. While

[87] Graves and Stenos (2017)
[88] Stewart et al. (2017)
[89] Graves and Stenos (2017
[90] Graves et al. (2016)
[91] Dehhaghi et al. (2019)
[92] Graves, S. www.asid.net.au/documents/items/415
[93] Stewart et al. (2017)
[94] Stewart et al. (2017)
[95] Graves and Stenos (2017)
[96] Dehhaghi et al. (2019)
[97] Graves and Stenos (2017)
[98] Stewart et al. (2017)

QTT is not known to directly affect the central nervous system, there have been reports of confusion, seizures and hallucinations as a prominent feature of this disease[99, 100]. There are no known identified risk factors for developing severe disease or complications of QTT[101].

Fever: High grade fever of up to 41°C is observed in acute cases. Prolonged fever is associated with rickettsaemia, end organ dysfunction and intensive care admissions[102].

Rash: Rash morphology is variable, and can be macular, maculopapular, vesicular or pustular, with the latter two forms sometimes confused with acute varicella. Infrequently the rash is pruritic. The rash usually lasts for 10–12 days, can appear as early as 24 hours after a tick bite and typically follows a widespread, global eruption involving the trunk and limbs. EM at and around the *Ixodes* attachment site is not uncommon in QTT[103]. Of note, EM is observed in other tick- borne illnesses such as *Rickettsia* and *Borrelia* spp. including Lyme disease[104], hence the recommendation to seek advice from appropriate experts in vector-borne diseases.

In approximately 50–65% of *R. australis* infections, an eschar is seen, with the detection of an eschar being diagnostically valuable. It is, however, often difficult to find as it can occur in sites that can be missed on examination such as in the axilla or groin. Tender lymphadenopathy, usually localised to the region draining the tick bite or eschar occurs in approximately 70 percent of patients[105].

The clinical presentation of a case of QTT in rural Queensland published by RACGP provides advice to support GPs[106].

While post-infection fatigue, a well-known consequence of several infections including Ross River virus, Q fever and Epstein-Barr virus, is not yet widely recognised as a problem following rickettsial infection, it has been suggested by a study involving two large cohorts of fatigued and non-fatigued patients and a case report[107].

3.2.4. If QTT suspected, following advice from appropriate experts, start antibiotic therapy (see *Therapeutic Guidelines antibiotic*).

Early recognition and treatment is important in QTT. Early initiation of doxycycline is critical as a delay in appropriate antimicrobial therapy is associated with increased likelihood of progression to severe disease and complications[108]. Patients usually show marked clinical improvement after 48 hours of starting antimicrobial therapy[109]. See section 6.2 for further detail on initial management.

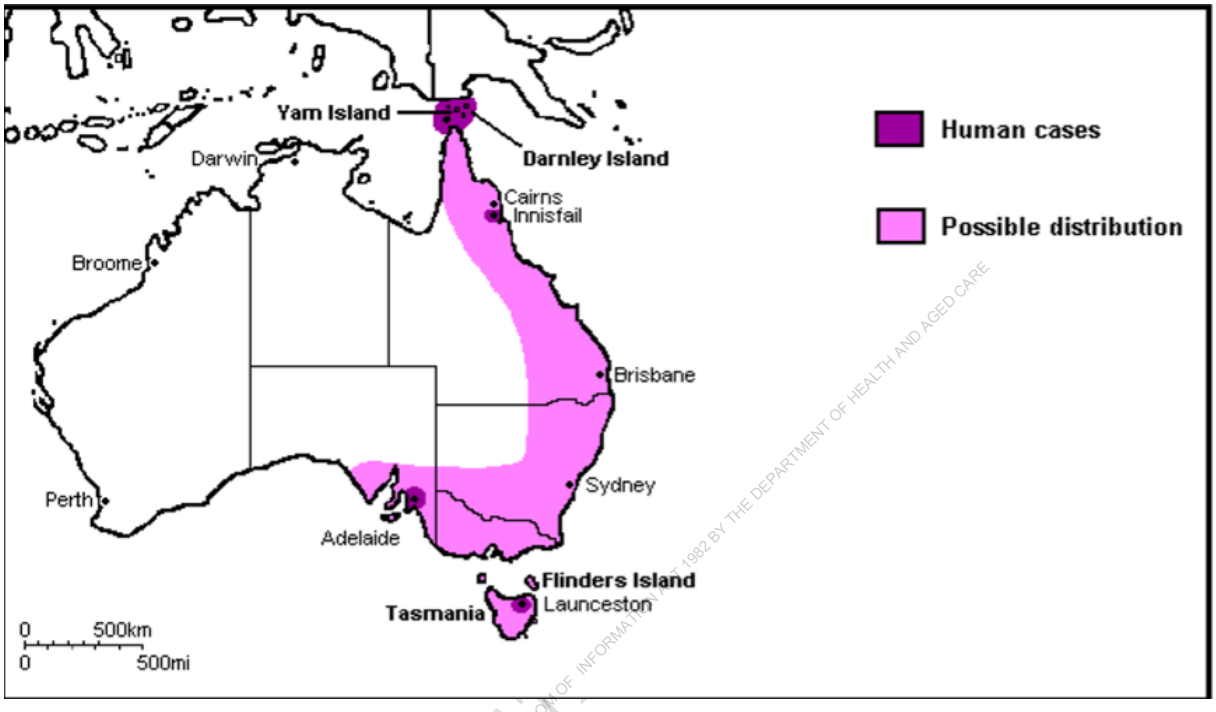
[99] Stewart et al. (2017)
[100] CDNA (2018)
[101] Stewart et al. (2017)
[102] Stewart et al. (2017)
[103] Stewart et al. (2017)
[104] Stewart et al. (2017)
[105] Stewart et al. (2017)
[106] Thomas and Wu (2018)
[107] Graves and Stenos (2017)
[108] Stewart et al. (2017)
[109] Stewart et al. (2017)

3.2.5. Australian Spotted Fever (ASF)

Geographical distribution

Australian spotted fever has been reported in the eastern half of Australia and is common in subtropical and tropical areas of Queensland extending down the east coast to East Gippsland in Victoria[110,111,112].

Figure 2: Distribution of Australian spotted fever[113]



Clinical presentation

Symptoms of Australian spotted fever include fever, headache and muscle aches with a stiff neck, vomiting and mental confusion also being possible[114].

3.2.6. Flinders Island Spotted Fever (FISF)

Geographical distribution

Flinders Island Spotted Fever is transmitted by the tick *Bothriocroton hydrosauri* and has been reported in Flinders Island Tasmania, Southern-eastern Australia, south-western coastal areas of Western Australia in Salisbury Island and Walpole, and south-eastern coastal regions of South Australia near Adelaide[115,116].

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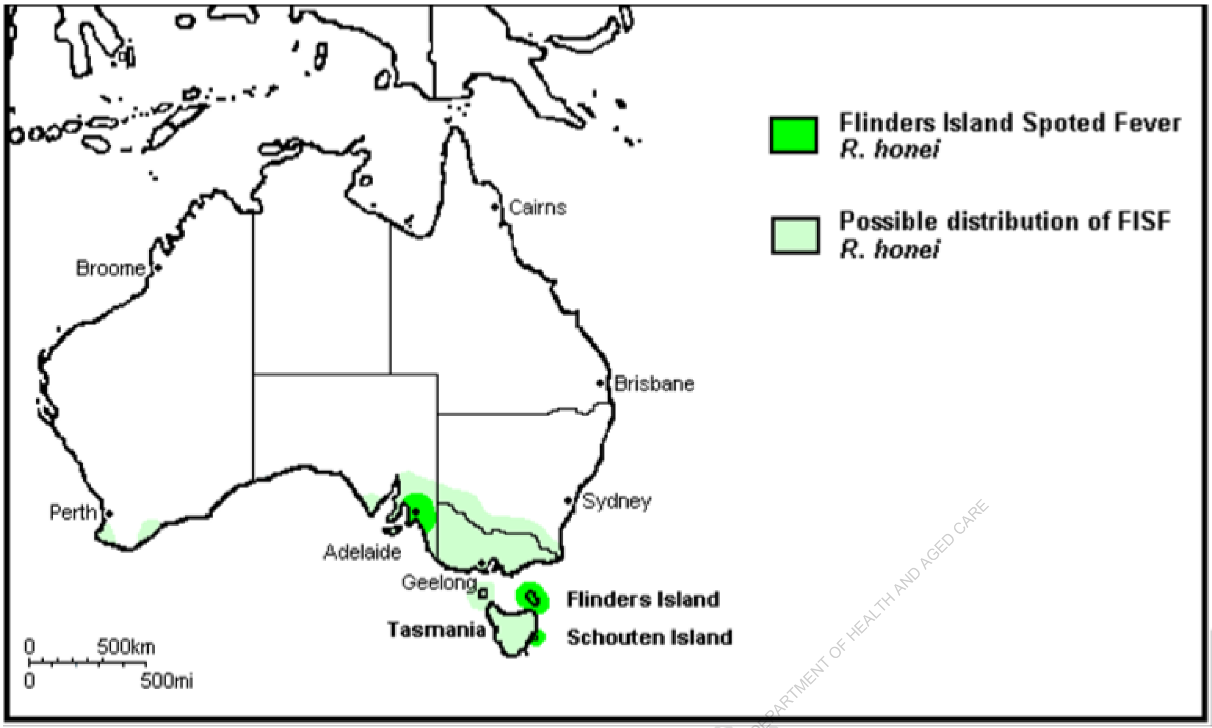
[110] Dehhaghi et al. (2019)
[111] Graves and Stenos (2017)
[112] Chalada et al. (2016)
[113] Graves, S. www.asid.net.au/documents/item/415
[114] Banks and Hughes (2019)
[115] Dehhaghi et al. (2019)
[116] Graves and Stenos (2017)

Figure 3: Distribution of Flinders Island Spotted Fever[117]



Clinical presentation

Symptoms of FISF include cough, fever, headache, maculopapular rash, myalgia and arthralgia[118].

3.2.7. Q fever

In Australia, Q fever is a nationally notifiable disease, with a Q fever laboratory case definition[119] and is included in the CDNA National Guidelines for Public Health Units[120]. In Australia, Q fever is the most commonly reported zoonotic disease[121]. As Q fever can be mistaken for other conditions, including other zoonotic diseases (for example, leptospirosis, brucellosis), the work up should be determined by a detailed history, examination and initial screening investigation, with a useful algorithm having been developed for general practitioners[122].

Transmission and geographical distribution

Q fever is acquired via various modes of transmission, a minority of which is tick-borne. While *Coxiella burnetii* are present in both the paralysis tick and ornate kangaroo tick, and therefore it is classified as a tick-borne disease, most cases of Q fever infection occur by inhalation of infectious aerosols from carrier (reservoir) vertebrate animals such as goats, sheep cattle, kangaroos and

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[117] Graves, S. www.asid.net.au/documents/item/415
[118] Dehhaghi et al. (2019)
[119] Public Health Laboratory Network (November 2017)
[120] CDNA (2018)
[121] Eastwood et al. (2018)
[122] Eastwood et al. (2018)

domestic pets or dust particles[123,124, 125, 126] contaminated by birth fluids, faeces or urine from infected animals. Rats may also harbour the tick *Amblyomma triguttum triguttum* which is a natural host for the *Coxiella burnetii* bacterium that causes Q fever in humans. The organism can remain dormant in soil and dust and spread by vehicle movements and activities such as lawn mowing or spread over wide areas under the influence of the wind and result in disease outbreaks[127].

The incubation period is typically 2-3 weeks; person to person spread rarely occurs[128]. Persons at increased risk of Q fever are:

- at risk occupational groups with contact of high risk animal products, including (but not limited to: abattoir and meat workers; agriculture, livestock and dairy farmers/workers; laundry workers handling clothes of at-risk workplaces; veterinary professionals and staff; animal shooters/hunters; dog/cat breeders and anyone regularly exposed to parturient animals;
- other people through non-occupational, environmental exposures including (but not limited to): family members of occupationally exposed groups; people living on in in close proximity to a high risk industry (neighbouring livestock farms and stockyards); visitors to at risk environments; people involved in mowing which aerosolises dust potentially contaminated by animal excreta; and
- persons at increased risk for chronic Q fever after experiencing an acute infection including: immunosuppressed persons; pregnant women; persons with valvular heat disease/valvular prosthesis; persons with aneurysms/vascular grafts[129].

In 2016, there were 551 cases (2.3 per 100,000 population) in the annual Q fever notification. The majority of Australian Q fever notifications were reported from Queensland and New South Wales during 2011–2015, with the notification rate remaining highest in south west/central west Queensland and northwest New South Wales, and generally reflecting the intensity of local cattle, sheep, and goat husbandry, and associated processing industries[130], although it is emerging in other regions, including Northern Territory and southwest Western Australia[131].

Clinical presentation

Q fever may present as an acute or chronic illness, with the majority (60%) of cases with asymptomatic/subclinical presentations[132,133]. People who do become sick often have a severe flu-like illness.

[123] Dehhaghi et al. (2019)
[124] McKenzie (2013)
[125] Graves and Stenos (2017)
[126] CDNA (2018)
[127] Eastwood et al. (2018)
[128] CDNA (2018)
[129] CDNA (2018)
[130] CDNA (2018)
[131] Dehhaghi et al. (2018)
[132] CDNA (2018)
[133] Chalada et al. (2016)

Acute Q fever

The most common manifestation is an influenza-like illness which might occur in conjunction with abnormal liver function tests, hepatitis and/or pneumonia. It can appear similar to other aetiologies of atypical pneumonia, such as those associated with *Legionella* or *Mycoplasma,* requiring consideration of differential diagnoses. Commonly reported signs and symptoms include: fever, chills, sweats, severe headache, (especially behind the eyes), photophobia, weakness, anorexia, nausea, myalgia, cough and weight loss[134, 135].

The most prevalent acute symptoms are fever (95%), headaches (53%) and myalgia (38%)[136].

In a minority of infected cases (≤1%), patients may develop pericarditis, myocarditis or neurologic complications (e.g., meningoencephalitis, encephalomyelitis)[137]. Unlike Rickettsial infections (see above), Q fever is unlikely to be associated with a rash[138].

Chronic Q fever

Chronic Q fever is the most serious form of the disease and can occur from one month to several years after acute illness as a result of persistence of *C. burnetii* infection in the host after primary infection[139, 140]. Sometimes there is no history of acute illness. Chronic Q fever may present as one of three forms according to the focus of infection: endocarditis; osteoarticular infections; and vascular infections with the abdominal or thoracic aorta the most frequent site for vascular infections[141]. Chronic Q fever may also manifest as chronic hepatitis, pericarditis, and very rarely as adenopathies, lung or splenic pseudotumours, or chronic neuropathy[142]. As such, Q fever may therefore sometimes present as an infection similar to Lyme carditis or Lyme neuroborreliosis[143].

Q fever fatigue syndrome

Q fever fatigue syndrome (QFS) refers to systemic symptoms that fail to recover more than 12 months after the acute illness and is the most common sequela following acute infection in Australia, occurring in approximately 10–15% of patients. The initial infection may be mild or severe, and patients present with a 'chronic fatigue-like' picture[144]. Typical features include: profound fatigue, arthralgia, myalgia, concentration and memory problems, sleeping problems, sweats and headaches[145]. Alcohol intolerance is a commonly reported feature[146]. The severity of the initial acute infection is the only known risk factor for the development of the post-Q-fever fatigue[147].

[134] Eastwood et al. (2018)
[135] CDNA (2018)
[136] Chalada et al. (2016)
[137] CDNA (2018)
[138] Dehhaghi et al. (2019)
[139] CDNA (2018)
[140] Eastwood et al. (2018)
[141] CDNA (2018)
[142] Chalada et al. (2016)
[143] Chalada et al. (2016)
[144] Eastwood et al. (20108)
[145] CDNA (2018)
[146] Eastwood et al. (2018)
[147] Eastwood et al. (2018)

3.2.8. If Q fever suspected clinically (appropriate symptoms AND at high risk epidemiologically), commence empirical treatment while waiting for laboratory tests.

While achieving a timely, definitive diagnosis of Q fever is challenging, early treatment is beneficial and empirical antibiotic therapy should be considered if the presentation and clinical history suggest a zoonotic disease[148]. Moreover, the Q fever CDNA guidelines for Public Health Units specify that if Q fever is suspected clinically (in people with appropriate symptoms AND who are at high risk of contracting Q fever), empirical treatment should be commenced without waiting for laboratory tests[149]. Refer to *Therapeutic Guidelines antibiotics* and section 6.2 for further detail.

3.3. Tick-borne disease not acquired in Australia

Tick-borne encephalitis

Tick-borne encephalitis (TBE) is a human viral infectious disease transmitted by the bite of infected ticks that attacks the central nervous system and can result in long-term neurological symptoms, complications and in some cases death[150,151]. It occurs in many parts of Europe and Asia and has become a growing public health challenge in Europe and other parts of the world[152]. People with recreational or occupational outdoor activities in woodland habitats in endemic areas are potentially at risk by contact with infected ticks[153].

There is no evidence it exists in Australia outside from those who have been infected overseas, but TBE has been characterised in an Australian man following a six-week trip through Russia[154].

Transmission and geographical distribution

TBE is caused by a virus (*Flavivirus* genus, family Flaviviridae) transmitted by the bite of infected *Ixodes* ticks, found in woodland habitats and occurs in many parts of Europe and Asia[155]. TBE may also be transmitted by the consumption of unpasteurised/raw milk and dairy products[156,157].

There are three subtypes of the TBE virus

- European subtype, transmitted by *Ixodes ricinus* ticks, endemic in rural and forested areas of central, eastern and northern Europe;
- Far eastern subtype, transmitted mainly by *I. persulcatus* endemic in far-eastern Russia and in forested regions of China and Japan; and
- Siberian subtype, transmitted by *I. persulcatus,* endemic in Urals region, Siberia and far-eastern Russia, and also in some areas in north-eastern Europe.

[148] Eastwood et al. (2018)
[149] CDNA (2018)
[150] Dehhaghi et al. (2019)
[151] European Centre for Disease Prevention and Control. Factsheet about tick-borne encephalitis (TBE)
[152] European Centre for Disease Prevention and Control. Factsheet about tick-borne encephalitis (TBE)
[153] European Centre for Disease Prevention and Control. Factsheet about tick-borne encephalitis (TBE)
[154] Dehhaghi et al. (2019)
[155] European Centre for Disease Prevention and Control. Factsheet about tick-borne encephalitis (TBE)
[156] Dehhaghi et al. (2019)
[157] European Centre for Disease Prevention and Control. Factsheet about tick-borne encephalitis (TBE)

Clinical presentation

The incubation period of TBE is seven days, on average, but may be up to 28 days. After foodborne infection, the incubation period is shortened, at around four days[158].

Approximately two-thirds of human TBE virus infections are non-symptomatic. In clinical cases, TBE most often manifests as a two-phased illness.

- Phase 1 is associated with non-specific symptoms (fever, fatigue, headache, myalgia, nausea) and lasts approximately five days (range 2-10 days).
- Phase 2 occurs after an asymptomatic interval of seven days (range 1-33 days) following Phase 1 and involves the central nervous system with symptoms of meningitis, meningoencephalitis, myelitis, paralysis, radiculitis[159].

Differences in severity of disease and mortality rates exist for the three subtypes. The far eastern subtype is associated with more severe disease[160].

3.4. Patients presenting with persistent debilitating symptoms and no diagnosis

3.4.1. If tick-borne disease is not indicated, consider alternative diagnoses.

Take care to identify any potentially treatable illness.

The diagnosis of MUS, including DSCATT, is a diagnosis of exclusion and requires ongoing review as new symptoms arise or treatments are trialled. A full history and examination are critical.

A clue to the underlying cause may be found in the particular symptom cluster, time course of symptoms, family history, social history, medications, travel or occupation.

Develop a differential diagnosis with consideration of the following causes:

- infectious - including blood borne or sexually transmitted infections, vector borne diseases, travel related, food and water borne
- autoimmune – including rheumatoid arthritis, motor neurone disease, multiple sclerosis
- neoplastic
- psychological – including depression, anxiety and reactions to traumatic events
- inflammatory
- vascular
- lifestyle related – including diet, exercise, sleep and stress, or
- genetic.

[158] European Centre for Disease Prevention and Control. Factsheet about tick-borne encephalitis (TBE)
[159] European Centre for Disease Prevention and Control. Factsheet about tick-borne encephalitis (TBE)
[160] European Centre for Disease Prevention and Control. Factsheet about tick-borne encephalitis (TBE)

4. DIAGNOSTIC TESTING

4.1. Lyme disease

4.1.1. Refer for laboratory testing for Lyme disease using a two-tier serology test in a NATA/RCPA accredited laboratory.

There is established Australian guidance for diagnostic laboratory testing for Lyme disease[161]. Diagnostic testing for Lyme disease should only be initiated following advice from appropriate experts such as a consultant physician practising in his or her speciality of infectious diseases or a specialist pathologist in his or her speciality of microbiology and should only be undertaken in Australia in a pathology laboratory accredited by NATA/RCPA to conduct such testing. If Lyme disease is being considered, patients should be referred for Lyme disease serology to your regular Approved Pathology Practitioner (APP).

Laboratory testing is essential to diagnose Lyme disease in Australia

In a non-endemic country for Lyme disease, (for example, Australia), it is not possible to reliably diagnose Lyme disease on clinical symptoms and signs alone. Laboratory testing is essential, as many other infectious and non-infectious diseases can have similar features to Lyme disease and all stages of Lyme disease have features that mimic other medical conditions[162].

Infection with *B. burgdorferi s.l.* leads initially to an IgM antibody response, followed two weeks later by an IgG antibody response. The IgM response tends to be relatively short-lived in most patients, but the IgG remains for decades following infection[163].

In a 2019 review of European and American guidelines (16 guidelines from seven countries) for the diagnosis of Lyme disease all guidelines indicated that the diagnosis of Lyme disease is currently based on a two-tier serology at all stages of infection, except for the early localised dermatological presentation known as EM[164]. While the recommendation from 15 of the 16 international guidelines was no serology testing in the case of EM suspicion due to early serology not being sensitive enough (40% to 60%) to confirm Lyme diagnosis at the EM stage[165], in Australia, where Lyme disease in not endemic diagnostic testing is recommended.

In Australia, laboratory diagnostic testing for Lyme disease is required for two reasons:

- Unless the clinician is familiar with the pathognomonic EM rash, it is clinically safer to obtain supportive evidence of infection through diagnostic testing (culture or PCR of the tissue or more usually antibody testing on a convalescent sample).
- Diagnostic laboratory support is preferred for patients presenting with non-specific signs and symptoms of a disease syndrome, notwithstanding the limitations of the tests.

[161] RCPA (May 2019)
[162] RCPA (May 2019)
[163] McKenzie (2013)
[164] Eldin et al. (2019)
[165] Eldin et al. (2019)

In 2019 IDSA/AAN/ACR advises:

- Serologic (serum antibody) testing is highly sensitive in patients with non-cutaneous manifestations of Lyme disease, as these manifestations typically develop after weeks to months of infection.
- Serologic testing is also highly specific when performed and interpreted according to current guidelines.
- Predictive value is increased when results are correlated with clinical features, patient history and risk factors.
- Currently, the only FDA-cleared or approved diagnostic assays for Lyme disease are antibody tests.

4.1.2. Commercially available laboratory testing methods to be avoided

Measurement of CD57 lymphocytes (by flow cytometry) and PCR for Lyme disease on urine samples is not recommended in the laboratory diagnosis of Lyme disease in Australian laboratories[166]. IDSA/AAN/ACR[167] concurred in 2019, advising that some commercially available laboratory testing methods including non-standard serology interpretation, urine antigen or DNA testing, or the use of lymphocyte transformation test or a quantitative CD57 lymphocyte assay should be avoided for clinical use due to lack of systematic, independent, reproducible validation studies.

NATA/RCPA Accredited Laboratories

The current standard laboratory protocol for diagnosing Lyme disease in Australian Diagnostic Laboratories follows international best practice and uses a two-tier serology system, the first stage involving screening with an enzyme-linked immunosorbent assay (ELISA) and, if positive, followed by an immunoblot assay (Western blot).

In Australia, the National Serology Reference Laboratory (NRL) review of serological assays to diagnose Lyme disease determined the tests used by accredited laboratories to diagnose Lyme disease had equivalent reliability to tests used in overseas laboratories[168], meaning Australian NATA/RCPA accredited laboratories are able to confidently diagnose classical Lyme disease acquired in patients who have travelled to endemic areas[169] and have contracted the infection more than four weeks prior to testing, noting that most patients seroconvert within four to eight weeks of infection[170]. A follow up paper to the NRL report noted that in the known negative population, specificities of the immunoassays ranged between 87.7% and 99.7% and in Australia's low prevalence population, this would translate to a positive predictive value of <4%[171].

While the NRL report confirmed that Australian laboratories have equivalent reliability to tests used in overseas laboratories, tests for Lyme disease have limitations whether internationally or in Australia (see section 4.1.3). Note that diagnostic tests conducted overseas are not covered under Australia's Medicare arrangements.

[166] RCPA (May 2019)
[167] Lantos et al. (2019)
[168] NRL (2017)
[169] RCPA (May 2019)
[170] RCPA (May 2019)
[171] Best et al. (2019)

4.1.3. Provide advice to patients about the tests for Lyme disease.

NICE recommends clinicians provide the following information to patients being tested for Lyme disease.

- Tests for Lyme disease have limitations and that false-positive and false-negative results can occur and what this means.
- Most tests for Lyme disease assess for the presence of antibodies and the possible reduction of accuracy of the test if:
  - testing is carried out too early (before antibodies have developed), and
  - the person has reduced immunity, for example in people on immunosuppressant treatments, which might affect the development of antibodies.
- The symptoms and signs associated with Lyme disease overlap with those of other conditions.
- They will be assessed for alternative diagnoses if their tests are negative and their symptoms have not resolved.
- Symptoms such as tiredness, headache and muscle pain are common and a specific medical cause is often not found[172].

4.2. Tick-borne disease known to be acquired in Australia

4.2.1. Refer for testing for known Australian tick-borne diseases

For patients presenting with tick bite and systemic symptoms (e.g. fever) consult with an appropriate expert in tick-borne diseases such as a pathologist or microbiologist with diagnostic expertise for appropriate test referral and follow advice for requests for testing for known Australian tick-borne infections and treatment of infections found. If the results do not show arthropod borne infection, consider an alternative diagnosis.

Queensland tick typhus (QTT)

Serological assays remain the main diagnostic test modality for diagnosing rickettsial infections. Currently, the indirect microimmunofluoresence assay (IFA) is considered the gold standard assay for diagnosing QTT. Acute and convalescent serum samples are taken 10-14 days apart and a four-fold rise in SFG antibody titre or a single positive titre of 1:256 is used to indicate acute or recent infection[173].

See also Update on Rickettsial infections[174].

Australian Spotted Fever

See Update on Rickettsial infections[175].

Flinders Island Spotted Fever

See Update on Rickettsial infections[176].

[172] NICE (April 2018a)
[173] Stewart et al. (2017)
[174] Graves, S. www.asid.net.au/documents/item/415
[175] Graves, S. www.asid.net.au/documents/item/415
[176] Graves, S. www.asid.net.au/documents/item/415

Q fever

The Q fever *National Guidelines for Public Health Units* developed by the Communicable Diseases Network of Australia (CDNA) specify that, if acute Q fever infection is suspected, a series of blood specimens should be requested and should include:

- unclotted blood or serum for Q fever PCR (and possible culture) AND
- paired (acute and convalescent) serum/clotted blood specimens taken 2-3 weeks apart for serology.

The collection of convalescent sera from all cases is critical, even if the patient has since recovered. See Q fever CDNA *National Guidelines for Public Health Unit*s section 8 Laboratory testing for specific detail).[177]
https://www1.health.gov.au/internet/main/publishing.nsf/Content/56DFBAB23468BF71CA2583520001F02F/$File/Q-fever-SoNG2018.pdf

4.3. Tick-borne disease not acquired in Australia

Tick-borne encephalitis

Seek advice from appropriate experts in vector-borne disease including pathologists with diagnostic experience and ID physicians.

4.4. Patient presenting with unresolved debilitating symptoms and no diagnosis

Investigations should be underpinned by clinical evidence. International evidence indicates patients with MUS are at risk of potentially harmful additional testing and are often subjected to repeated diagnostic investigations, and unnecessary and costly referrals and interventions. Unnecessary investigations that do not show anything, are often not reassuring. They can make someone worry even more that there is something still to be found and more tests are needed.

For fatigue, diagnostic testing is determined by the differential diagnosis as per normal clinical practice[178].

[177] CDNA (2018)
[178] Murtagh J. (2003)

5. DIAGNOSIS

5.1. Lyme disease

Lyme disease is not a notifiable disease in Australia.

5.1.1. Confirmed diagnosis

A confirmed case of Lyme disease in Australia requires laboratory evidence AND clinical evidence AND epidemiological evidence.

The Royal College of Pathologists of Australasia notes that caution is important in dealing with specimens for Lyme disease testing and in interpreting of positive or indeterminate laboratory results and advises that medical microbiologists should add explanatory comments to all such reports to assist the referring doctor to interpret the laboratory findings correctly[179].

In addition to the sensitivity and specificity of the diagnostic tests recommended in international guidelines for Lyme disease, the prevalence of the disease or the pre-test probability of a disease strongly influences interpretation of any diagnostic test result. In a region where Lyme disease is uncommon, patients with highly characteristic clinical presentations are rarely found to have Lyme disease and positive test results are seldom associated with clinically probable infection, although the negative predictive value of Lyme disease testing will be very high[180]. In an area of low Lyme disease incidence in the US, a study of Lyme disease testing showed an 80% false-positive rate which puts patients at risk of incorrect Lyme diagnoses and adverse drug reactions from inappropriate treatment[181]. Therefore, awareness of epidemiological context and the absence of an alternative diagnosis are necessary for a clinician to decide whether a positive test is explanatory or coincidental. The difficulties in interpreting diagnostic tests for Lyme disease as described above, coupled with the difficulties clinicians in Lyme endemic countries experience in diagnosing Lyme disease[182] underpin the recommendation that medical professionals seek advice from appropriate experts in infectious diseases or pathology.

5.1.2. No confirmed diagnosis of Lyme disease and symptoms resolve

If the immunoblot test for Lyme disease is negative and symptoms have resolved, explain to the patient that no treatment is required[183].

5.1.3. No confirmed diagnosis of Lyme disease and symptoms persist

If the immunoblot test for Lyme disease is negative (regardless of the ELISA result) but symptoms persist, NICE recommends considering a discussion with, or referral to, a specialist appropriate to the patient's history and symptoms (for example, adult or paediatric ID physician, rheumatologist or neurologist) to:

[179] RCPA (May 2019)
[180] Lantos et al. (2015a)
[181] Lantos et al. (2015a)
[182] Brunton et al. (2017)
[183] NICE (April 2018a)

- review whether further testing may be required for suspected Lyme disease (for example, synovial fluid aspirate, or biopsy, or lumbar puncture for cerebrospinal fluid analysis; OR
- consider alternative diagnoses including both infectious (including other tick-borne diseases) and non-infectious diseases[184].

5.2. Tick-borne diseases known to be acquired in Australia

Queensland Tick Typhus

For diagnosis of QTT, laboratory investigations of cases include:

- mild-to-moderate thrombocytopaenia commonly early in the disease course transforming into a reactive thrombocytosis during recovery from the disease
- a transient and mild elevation of hepatic transaminases early in the disease
- leukopenia in mild cases
- neutrophilia and toxic changes on blood film in patients presenting with severe infection, and
- significantly raised C-reactive protein measurements in systemic ricktettsial infection in contrast to uncomplicated viral infections[185].

A number of factors can complicate the diagnosis.

- Substantial cross-reactivity of antibodies can occur between some rickettsia and with other species of bacteria such as *Proteus* and *Legionella.*
- Concomitant illnesses such as rheumatologic- and immune-mediated disorders can yield false-positive rickettsial serological tests.
- Occasionally, patients infected with *R. australis* do not seroconvert.
- Serology tests can be difficult to interpret in acute illness; low level titres are associated with previous SFG *Rickettsia* exposure and to a patient's current nonrickettsial infection[186].

Initial negative serological studies do not rule out rickettsial infection and should not alter treatment completion in potentially infected patients[187].

See also Update on Australian Rickettsial Infections[188].

Australian Spotted Fever

See Update on Australian Rickettsial Infections[189].

[184] NICE (April 2018a)
[185] Stewart et al. (2017)
[186] Stewart et al. (2017)
[187] Thomas and Wu (2018)
[188] Graves, S. www.asid.net.au/documents/item/415
[189] Graves, S. www.asid.net.au/documents/item/415

Flinders Island Spotted Fever

See Update on Australian Rickettsial Infections[190].

Q fever

Diagnosis of Q fever can be made by a medical professional based on symptoms, clinical examination, and laboratory tests on blood samples. Two or more blood samples on separate occasions are often required to confirm a Q fever diagnosis[191].

CDNA provide details on laboratory tests (PCR and serology testing) and interpreting results for Q fever[192].

Advice by RACGP to assist GPs in diagnosing Q fever, including in aspects of diagnostic tests is also available[193].

5.3. Tick-borne disease not acquired in Australia

Tick-borne encephalitis

Diagnosis of TBE is based on detection of specific IgM antibodies in cerebrospinal fluid (intrathecal production) and/or serum, mainly by ELISA. TBE antibodies appear six days after onset and are usually detected when neurological symptoms are present[194].

5.4. Patient presenting with debilitating symptoms - diagnosis of specific disease(s) is established

Where a specific disease or diseases are diagnosed, with or without specialist input, treat accordingly, as per usual clinical practice. When symptoms resolve, the patient exits this DSCATT Clinical Pathway.

5.5. Patient presenting with debilitating symptoms - no diagnosis is established and medically unexplained symptoms persist

If no diagnosis of a specific disease(s) is established through this phase of the pathway and symptoms persist, move to next phase, the stepped care approach.

People with MUS may obtain a diagnosis over time as symptoms develop and guide to the origin of the illness. Others may find that symptoms resolve over time without ever identifying a cause.

[190] Graves, S. www.asid.net.au/documents/item/415
[191] CDNA (2018)
[192] CDNA (2018)
[193] Eastwood et al. (2018)
[194] European Centre for Disease Prevention and Control. Factsheet about tick-borne encephalitis (TBE)

6. INITIAL MANAGEMENT

6.1. Lyme disease

6.1.1. International guidelines for the treatment of Lyme disease

Lyme disease is treated with antimicrobials from several classes with activity against *B. burgdorferi,* including doxycycline, penicillin, amoxicillin, cefuroxime, ceftriaxone and azithromycin, with the goals of treatment being the resolution of objective signs and symptoms of infection with prevention of relapsed active infection or new complications of infection. Under most circumstances, oral therapy is effective and preferred over intravenous therapy due to equivalent efficacies, tolerability, and cost[195].

Treatment recommendations, based on available randomised controlled trials (RCTs) published by American professional bodies such as the IDSA, the American Academy of Paediatrics and a variety of national and supranational associations in Europe (EUCLAB) indicate that the approaches to therapy are largely similar on both sides of the Atlantic with some minor differences in the recommended dosage and treatment duration[196].

The majority of international guidelines, including IDSA[197, 198], NICE[199] and IDSA/AAN/ACR[200] recommend one course of antibiotic therapy for all presentations of Lyme disease.

The NICE guideline covers diagnosing and managing Lyme disease, and aims to raise awareness of Lyme disease should it be suspected, and ensure people have prompt and consistent diagnosis and treatment. The recommendations aim to standardise antibiotic treatment and to provide a consistent framework for good practice in managing Lyme disease[201].

The latest guidelines from NICE (2018) recommend antibiotic therapy of 21 days for all presentations except Lyme arthritis (28 days).

The 2018 NICE guidelines were underpinned by the following evidence-based reviews:

- Management of erythema migrans[202]
- Management of non-specific symptoms related to Lyme disease[203]
- Management of neuroborreliosis[204]

[195] Lantos et al. (2019)
[196] Borchers et al. (2015)
[197] Wormser, Gary P., Raymond J. Dattwyler, Eugene D. Shapiro, John J. Halperin, Allen C. Steere, Mark S. Klempner, Peter J. Krause, et al. (November 1, 2006).
[198] Lantos, Paul M., William A. Charini, Gerald Medoff, Manuel H. Moro, David M. Mushatt, Jeffrey Parsonnet, John W. Sanders, and Carol J. Baker. (July 2010)
[199] NICE (April 2018a)
[200] Lantos et al. (2019)
[201] NICE. (April 2018a)
[202] NICE (April 2018c)
[203] NICE (April 2018d)
[204] NICE (April 2018e)

- Management of Lyme arthritis[205]
- Management of Acrodermatitis chronica atrophicans[206], and
- Management of Lyme carditis[207].

Subsequent to the 2018 NICE guidelines, draft clinical practice guidelines for the prevention, diagnosis and management of Lyme disease were published by IDSA/AAN/ACR, with the recommendations informed by a systematic review and an assessment of the benefits of harms and alternative care options. In contrast to NICE recommendations, IDSA/AAN/ACR recommended for patients with EM, treat with either a 10-day course of doxycycline or a 14-day course of amoxicillin, cefuroxime axetil or phenoxymethylpenicillin rather than longer treatment courses (**strong recommendation; moderate quality of evidence**)[208]. The systematic review found no clinical evidence to support regimens intended to treat fastidious states of *B. burgdorferi* infection, such as morphologic variants (aka "cyst" forms, "round" bodies, or "L-forms"), or to treat biofilms[209].

6.1.2. Relevance of international guidelines to the Australian setting

International treatment guidelines may not be entirely applicable in the Australian health care setting even in patients whom have a travel history overseas to an endemic area.

Treatment for Lyme disease in the Australian health care context should only be initiated based on the expert advice of either a consultant physician practising in his or her speciality of infectious disease or a specialist pathologist in his or her speciality of microbiology. This advice will be based upon results of confirmatory testing conducted in a NATA/RCPA accredited laboratory and/or other clinical findings relevant to informing a treatment decision.

6.1.3. Therapeutic modalities not recommended for treatment of patients with any manifestation of Lyme disease

There is no evidence to support the use of combination antibiotics, immunoglobulin, hyperbaric oxygen, specific nutritional supplements or prolonged courses of antibiotics for the management of Lyme disease[210,211,212].

IDSA does not recommend the following therapeutic modalities for treatment of patients with any manifestation of Lyme disease because of a lack of biologic plausibility, lack of efficacy, absence of supporting data, or the potential for harm to the patient:

- first-generation cephalosporins, fluoroquinolones, carbapenems, vancomycin, metronidazole, tinidazole, amantadine, ketolides, isoniazid, trimethoprim-sulfamethoxazole, fluconazole, benzathine penicillin G,

[205] NICE (April 2018f).
[206] NICE (April 2018g)
[207] NICE (April 2018h)
[208] Lantos et al. (2019)
[209] Lantos et al. (2019)
[210] Wormser, Gary P., Raymond J. Dattwyler, Eugene D. Shapiro, John J. Halperin, Allen C. Steere, Mark S. Klempner, Peter J. Krause, et al, (November 1, 2006)
[211] Klempner MS, Baker PJ Shapiro Ed, et al (2013)
[212] Borchers et al. (2015)

- combinations of antimicrobials,
- pulsed-dosing (i.e., dosing on some days but not others),
- long-term antibiotic therapy,
- empirical antibabesiosis therapy in the absence of documentation of active babesiosis
- anti-*Bartonella* therapies,
- hyperbaric oxygen,
- fever therapy (with or without malaria induction),
- intravenous immunoglobulin,
- ozone
- cholestyramine,
- intravenous hydrogen peroxide,
- vitamins and nutritional managements
- magnesium or bismuth injections[213]

The strength of recommendation and quality of evidence for this IDSA recommendation for the therapeutic modalities listed above was E-III (Strongly against; Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees)[214].

More recently a study in 2015 looking to identify websites of clinics that marketed nonantimicrobial therapies for Lyme disease identified more than 30 alternative treatments[215]. A review of the medical literature by the authors did not substantiate efficacy or in most cases any rational for the advertised treatments which fell into following several broad categories: oxygen and reactive oxygen therapy; energy and radiation-based therapies; nutritional therapy; chelation and heavy metal therapy; biological and pharmacological therapies ranging from certain medication without recognised therapeutic effects on *B. burgdorferi* to stem cell transplantation[216].

6.2. Tick-borne disease known to be acquired in Australia

Table 3: Initial treatment of Australian tick-borne diseases

Queensland tick typhus
QTT is readily treated with a short course of doxycycline. Early initiation of doxycycline is critical - a delay in appropriate antimicrobial therapy is associated with increased likelihood of progression to severe disease and complications. Doxycycline should be administered orally in mild-to-moderate infection and intravenously in severe infection. There are no published data on the importance of antibiotics in mild *R. australis* infection although early administration probably prevents hospitalisation and morbidity[217].

[213] Wormser et al. (2006)
[214] Lantos et al. (2015b)
[215] Lantos et a. (2015b)
[216] Lantos et al. (2015b)
[217] Stewart et al. (2017)

Patients usually show marked clinical improvement after 48 hours of antimicrobial therapy[218, 219].

Q Fever

The Q fever CDNA National Guidelines for Public Health Units specifies that if Q fever is suspected clinically, empirical treatment should be commenced without waiting for laboratory tests. [220] This recommendation is in the context of a patient with appropriate symptoms AND who are at high risk of contracting the disease.

Refer *Therapeutic guidelines: Antibiotics.* A two-week course of oral doxycycline is generally used to treat Q fever.

Flinders Island Spotted Fever and Australian Spotted Fever

Patients with Flinders Island Spotted Fever and Australian Spotted Fever are treated with Doxycycline. Refer *Therapeutic guidelines: Antibiotics.*

6.3. Tick-borne diseases not acquired in Australia

TBE

There is no specific antiviral therapy for TBE. Treatment relies on supportive management. Patients with meningitis, encephalitis or meningomyelitis require hospitalisation and supportive care based on syndrome severity[221]. Patients presenting with these severe symptoms are outside the scope of this Clinical Pathway.

6.4. Management of patients with persistent symptoms and who remain undiagnosed

This part of the pathway pertains to management of patients who have debilitating symptoms that cannot be attributed to tick-borne disease or another diagnosable condition.

Where there is no diagnosis and the patient is experiencing symptoms that are medically unexplained, it is especially important to ensure that person-centred care is provided that validates, addresses and manages their symptoms as well as possible.

The Australian Commission on Safety and Quality in Healthcare advises that "Person centred-care" involves

- seeking out and understanding what is important to the patient
- fostering trust
- establishing mutual respect and
- working together to share decisions and plan care[222].

[218] Stewart et al. (2017)
[219] Graves and Stenos (2017)
[220] CDNA (2018)
[221] European Centre for Disease Prevention and Control. Factsheet about tick-borne encephalitis (TBE)
[222] Australian Commission on Safety and Quality of Care (accessed 19 August 2019b)

Key dimensions include respect, emotional support, physical comfort, information and communication, continuity and transition, care coordination, access to care, and partnerships with patients, carers and family in the design and delivery of care[223].

Patients should be treated symptomatically and are also encouraged to consider the potential for harm with complementary medicines for which there is no evidence in those with comorbidities. All people with medically unexplained symptoms, (including those given the title DSCATT) can be assisted to have an improved quality of life with good care in a partnership between patient and the health care team.

International and Australian guidelines provide evidence-based, practical and consistent recommendations for people that can be applied to patients with DSCATT. Good communication and empathy are important. Patients' concerns need to be taken seriously and their symptoms acknowledged and alleviated.

The most common unexplained symptoms reported by patients experiencing DSCATT include fatigue, disordered thinking, sensory disturbance, arthralgia, headache[224]. These symptoms can have multiple different causes, depending on the particular symptoms, cluster, and time frame of symptom(s).

6.4.1. Practice Harm Minimisation

International evidence indicates patients with MUS are at risk of potentially harmful additional testing[225] and are often subjected to repeated diagnostic investigations, and unnecessary and costly referrals and interventions[226]. An analysis of the Senate submissions noted patients that identified as having DSCATT experience social and financial harms and are at risk of nosocomial harms and may also have sought alternative and potentially non-evidence-based diagnoses and treatments[227].

In managing MUS in general practice balancing the iatrogenic risk of investigation with the therapeutic risk of missing something important is a challenge for GPs[228].

Table 4: Recommendations for managing MUS

Avoid

• Repeated diagnostic testing.
  ○ Harms include worry that there is still something to be found that hasn't been tested for yet, increased likelihood of false positives, and the finding of minor, non-significant abnormalities in test results that increase anxiety.
• Use of non-accredited laboratories for diagnostic testing and use of unconventional diagnostic techniques e.g. kinesiology.
  ○ Harms include false positives and wrong diagnosis.
• Unnecessary referrals and interventions.

[223] Australian Commission on Safety and Quality of Care (accessed 19 August 2019a)
[224] Brown (2018)
[225] Olde Hartman et al. (2017)
[226] Joint Commissioning Panel for Mental Health. (2017)
[227] Brown (2018)
[228] Stone (2015)

- Harms include repeating and extending unnecessary testing and iatrogenic harm as well as financial costs.

- Treatments with known harm and no benefit e.g. long-term antibiotics, extreme diets, miracle mineral solution, hyperbaric oxygen treatments.
  - Harms include toxicity, hypersensitivity reactions, predisposition to Clostridium difficile infection, development of antibiotic resistance, line sepsis, severe and persistent vomiting and diarrhoea, and large financial cost without benefit.

Encourage

- Discussion of intended "natural" or alternative therapies for evaluation of individualised harms versus benefits.
  - An awareness of the evidence base and side effects to be aware of can assist patients in choosing alternative therapies wisely and avoiding unnecessary out of pocket costs and unintended harms.

- Periodic re-evaluation of symptoms and new symptoms to determine an identifiable cause and efficacy of treatment.
  - Small changes over time may not be noticed by patients. Review allows encouragement regarding improvements, detection of deterioration, and evaluation of new symptoms arising.

- Discussion of possible causes of and treatments for symptoms that have been found on the internet or recommended by friends.
  - Not having a diagnosis is difficult for patients in many ways and leads to a vulnerability to looking for a cause of their symptoms. The internet, social media and social contacts can be spreaders of both good and poor information. Remaining open to a patient discussing what they have found allows for education, exploration of misinformation, identification of reliable sources and identification of potential treatments to trial.

- Enlistment of other members of a multidisciplinary team.

- Consideration of mental health strategies.

In addition to the alternative and complementary therapies reviewed and not recommended for the treatment of Lyme disease (see section 6.1.3), many of which were reported by patients to the Senate Inquiry[229] to have been recommended to them, refer to NHMRC and Therapeutic Goods Administration (TGA) for information on complementary and alternative medicines in Australia.

Having a chronic medical condition of any cause increases the likelihood of mental health conditions, which in turn can lead to poorer outcomes. Acknowledging the difficulty of chronic symptoms and supporting the important mental health strategies is vital to person centred care in chronic disease[230].

6.4.2. Medically Unexplained Symptoms

Medically unexplained symptoms (MUS) are defined as physical symptoms persisting for more than several weeks and for which adequate medical examination has not revealed a condition that adequately explains the symptoms[231]. Patients with MUS may be very unwell and require complex

[229] The Senate Community Affairs References Committee (May 2016)
[230] Stone L. (2015)
[231] Olde Hartman TC et al (2017)

care. People experiencing debilitating symptoms attributed to ticks, without any definitive diagnosis could be considered to fall within the definition of MUS. A recent review of MUS guidelines in Europe[232] estimates that between 3-11% of patients visiting general practice repeatedly consult their GP for MUS. However, this finding might not be entirely applicable to Australia. MUS exist along a continuum ranging from self-limiting symptoms to recurrent and persistent symptoms through to symptom disorders.

Advice from the RACGP[233] and the review of the international MUS guidelines by Olde Hartman et al[234] summarising the five guidelines from the Netherlands, Denmark, UK and Germany (two of which provide evidence graded recommendations) is consistent. Patients with MUS often feel stigmatised and not taken seriously. To manage these concerns, all guidelines recommend:

- highlighting the importance of paying attention to the doctor-patient relationship;
- providing an individualised approach that recognises the patient's illness and taking the patient's symptoms seriously;
- demonstrating empathy with consultations aiming to validate the patient's distress;
- highlighting the importance of providing an explanation in the patient's language about the possible causes of their symptoms (Patients benefit from an explanation that makes sense, removes blame from the patient, generates ideas on how to manage the symptoms. The 2011 UK guidance published by the Royal College of General Practitioners in the UK, advises that GPs should be explicit about their thoughts, uncertainties and expectations of referrals to specialist care[235].); and
- caution that "*patients with persistent MUS suffer from their symptoms, are functionally impaired, and are at risk of potentially harmful additional testing and treatment*[236]".

A qualitative study into the experiences of patients identifying with chronic Lyme disease reported on the importance of actively engaged and sympathetic clinical encounters. They showed that where patient concerns are fully acknowledged and addressed, they experience greater satisfaction with their healthcare[237].

6.4.3. The Stepped Care Model

The challenge for the GP involves managing individual symptoms, but also creating a framework for the chronic care of patients with significant ongoing illness[238].

The stepped care model of care is internationally recognised and familiar to and widely used by GPs in Australia in all aspects of patient care. The model is recommended for use in patients with MUS by international and Australian guidelines.

Stepped care is an evidence-based, staged system comprising a hierarchy of interventions, from the least to the most intensive, matched to the individual's needs. Within a stepped care approach

[232] Olde Hartman TC et al (2017)
[233] Stone L (2015)
[234] Olde Hartman TC et al (2017)
[235] Chitnis A, Dowrick C, Byng R, et al. (2011)
[236] Olde Hartman (2017)
[237] Ather A, (2014)
[238] Stone L (2015)

an individual will be supported to transition up to higher intensity services or transition down to lower intensity services as their needs change[239].

As background, four international guidelines in MUS recommend a stepped care approach to address three levels of severity of symptoms, which lack clear cut-off points. Throughout all 5 international MUS guidelines, it is seen as important that one care provider, preferably the GP, keeps control and co-ordinates the care process.

In addition to being recommended as an approach for managing care for people with MUS, the stepped care service model has been shown in RCTs to be effective for the management of chronic pain[240], and for the management of depression and anxiety[241] and in the assessment and management of anxiety and depression in adult cancer patients[242]. Stepped care models are widely used in the England, Scotland, USA, New Zealand and Australia.

In Australia, the stepped care model of care is familiar to and widely used by GPs in all aspects of patient care. GPs make assessments to determine the best management approach to guide their patients in accessing services appropriate to their level of need, and thus ensure that more intensive and often costly services are directed to patients best able to benefit from them[243]. While referrals are made to other relevant health practitioners as appropriate, it is important that one care provider, preferably the GP, coordinates care.

Stepped care models aim to:

- offer a variety of support options for people with different levels and types of need, from low intensity to high intensity
- provide clear pathways between these care options as individuals' needs change, and
- improve collaboration and integration between services[244].

Central to the stepped approach is the development of an individualised care plan, developed in discussion with the patient.

Table 5: Overview of Stepped Care approach to managing medically unexplained symptoms[245]

Step 1: For patients with mild functional limitations and who experience one or several symptoms
• Explore symptoms, conduct physical examination and or additional investigations. List the symptoms. • Summarise findings discussing clearly what was found and explicitly mentioning what was not found. • Try to reach a shared definitions of the problem. It is important to recognise the symptoms and the fact the patient is troubled by them. Explore and address anxieties and misconceptions. It is very important that the patient's concerns are treated seriously and in a sensitive manner. • Provide the patient with targeted and tangible information about ways to manage symptoms and an individualised care plan.
Step 2: For patients with moderate functional limitations with several symptoms, cluster symptoms or a symptom duration longer than expected

[239] General Practice Mental Health Standards Collaboration (GPMHSC) (2019)
[240] Department of Veterans Affairs, (2009)
[241] Australian Government, Department of Health, (accessed 19 August 2019)
[242] Butow P, Price MA, Shaw JM, Turner J, Clayton JM, Grimison P, Rankin N on behalf of the Psycho-oncology Co-operative Research Group (PoCoG), University of Sydney (2015) ,
[243] General Practice Mental Health Standards Collaboration (GPMHSC): (2019)
[244] GPMHSC (2019)
[245] Olde Hartman (2013)

- Continue GP led care as in Step 1 and if the patient is unable to expand his/her level of activity to an acceptable standard, refer to either primary or secondary care practitioners e.g. physiotherapy, nurse practitioners, specialist GPs, psychotherapy/CBT.
- Refer to secondary specialist services as required.
- Make regular follow-up appointments if functional limitation persists e.g. every 4-6 weeks.

Step 3: For patients with severe functional limitations and a large number of symptoms and duration of 3 months or more

- Refer to secondary, tertiary care providers and or multi-disciplinary teams or treatment centres.
- Continue to stimulate the expansion of the patient's functioning and monitor for deterioration in function.
- It is important that one care provider, ideally a GP, co-ordinates the care provided.
- Limit long term treatments and investigations that are not useful and may even be harmful.
- Make regular follow-up appointments during treatment e.g. 4–6 weeks.

International guidelines concur that doctor-patient communication is key they emphasise the importance of exploring patient's ideas, concerns and expectations, providing acceptable explanations, providing practical and constructive advice that is applicable to their daily lives is important and offering advice on symptom management. Considering the patient's ethical-cultural background in all steps is recommended[246].

[246] Olde Hartman TC et al. (2013)

7. ONGOING MANAGEMENT

7.1. Lyme disease

There is a strong body of evidence that does not support ongoing and long-term treatment of Lyme disease with antibiotics[247,248,249,250,251,252,253,254].

Prolonged intravenous or oral antibiotic therapy for Lyme disease is not recommended in managing patients with Lyme disease in Australia as studies performed in North America and Europe showed these therapies did not significantly improve outcomes and can be associated with significant adverse effects[255].

NICE reviewed the evidence for the management of ongoing symptoms related to Lyme disease and recommended that:

- For managing ongoing symptoms of Lyme disease after a course of antibiotics, patients should not be routinely offered more than two courses of antibiotics because of a lack of evidence of benefit.
- It is important to consider alternative diagnoses to prevent inappropriate antibiotic treatment and misdiagnosis and discussion with a specialist or referral should be considered for some people if a different tick-borne disease is possible.
- Healthcare professionals help people with long term symptoms related to Lyme disease to access support if needed[256].

NICE advised that current treatment of Lyme disease is a single course of antibiotics; however, people who have had treatment for Lyme disease sometimes report ongoing symptoms, the cause of which is often not clear and includes reinfection, or organ damage caused by Lyme disease which may take a long time to heal or may even be permanent[257].

The term 'ongoing symptoms' was preferred for the guideline as it does not attribute cause of symptoms; terms such as chronic Lyme disease imply possible chronic infection and may be misleading[258].

More recently IDSA/AAN/ACR recommended against additional antibiotic therapy for patients who have persistent or recurring non-specific symptoms such as fatigue, pain, or cognitive impairment following treatment for appropriately diagnosed Lyme disease, but who lack objective evidence of reinfection or treatment failure (**Strong recommendation; moderate**

[247] NICE (April 2018i)
[248] Borchers et al. (2015)
[249] Dessau et al. (2018)
[250] Sanchez et al. (2016)
[251] Shapiro et al. (2017)
[252] eTG antibiotics (June 2019 edition).
[253] NICE (April 2018i)
[254] Lantos et al. (2019)
[255] eTG antibiotics (June 2019 edition).
[256] NICE (April 2018a)
[257] NICE April 2018a)
[258] NICE (April 2018i)

quality evidence). The recommendation placed high value on avoiding harm due to unnecessary antibiotic exposure or to unnecessary IV access devices. IDSA/AAN/ACR noted the risks of these interventions were not matched by convincing evidence that antibiotics improved patients' symptom experience or quality of life any better than a placebo[259].

In Australia, an additional course of antibiotics will be determined on case by case basis. Full resolution of symptoms may take some time but does not require further antibiotics.

If symptoms have resolved, the patient exits the Clinical Pathway.

If symptoms persist, consider alternative diagnoses (see section 3.4).

7.2. Tick-borne disease known to be acquired in Australia

Queensland tick typhus (QTT)

Delay in correct antimicrobial therapy is associated with increased likelihood of progression to severe disease and complications. However, some individuals, for unknown reasons, progress to severe disease and sepsis despite early doxycycline therapy, with concurrent comorbidities, *Rickettsia* inoculum size and inherent virulence in rickettsial strains being suggested factors[260].

The literature indicates there is little systematic evidence on the outcomes of acute *R. australis* infection, particularly in non-hospitalised patients; however, where severe hospitalised cases with complications have been documented, a full recovery following acute illness is expected. Additionally, there is no evidence of chronic infection. A post infective syndrome of lethargy, malaise and muscle pains persisting for several months or more after acute infection, however, has been described[261].

If symptoms have resolved, the patient exits the Clinical Pathway.

If symptoms persist, consider alternative diagnoses (see section 3.4).

Q fever

After treatment of *C. burnetii* primary infection, CDNA guidance includes the following recommendations:

- screening for risk factors of chronic Q fever, including pre-existing valvular heart disease/valvular prosthesis, vascular aneurysms/vascular grafts and immunosuppression;
- undertaking a cardiac assessment to assess whether there are underlying abnormalities of the heart valves; and
- monitoring serologically and clinically at 3,6,9,12,18 and 24 months those who, after acute infection, are at higher risk of chronic Q fever.

Chronic Q fever requires prolonged treatment with antibiotics. Expert advice from an ID physician and other specialist physicians should be sought as appropriate[262].

If symptoms have resolved, the patient exits the Clinical Pathway.

If symptoms persist, consider alternative diagnoses (see section 3.4).

[259] Lantos et al. (2019)
[260] Stewart et al. (2017)
[261] Stewart et al. (2017)
[262] CDNA (2018)

7.3. Management of patients with persistent symptoms and who remain undiagnosed

The patient's GP will lead the ongoing management and review of symptoms. In the event of persistent dysfunction, evaluate the situation regularly and offer any new treatment options. The review and evaluation of new symptoms may require a change of level in stepped care for the patient.

If symptoms have resolved the patient exits the Clinical Pathway.

APPENDIX A: CASE STUDIES

Case Study 1 - Rickettsiae infection[263]

Mr A aged 51 years presented with a one-week history of fever, lethargy, anorexia and generalised arthralgia, with a rash and a dry scab, indicative of an insect bite, surrounded by a rash on his back. The patient was afebrile and had no other symptoms.

Further questioning revealed that he had visited the Bunya Mountains National Park, Queensland, for a hiking trip two weeks prior to presentation. He had not travelled overseas. The patient was not aware of being bitten by ticks or other insects. The GP suspected Queensland tick typhus, given this is a common presentation in patients with tick bites who have visited that area and started the patient on doxycycline 100 mg twice daily immediately and referred for tissue biopsy for histopathology and a serological immunofluorescence assay for *Rickettsia rickettsii* at 1:128 titre from an accredited laboratory.

The biopsy confirmed a mononuclear vasculitis consistent with rickettsial infection but the initial serology was negative. Other blood tests, including liver and renal function tests, were normal.

At review two weeks later, the patient reported that most of his symptoms had resolved and the rash had cleared. Some ongoing minor lethargy persisted. Rickettsial serology was repeated at this time (four weeks after likely bite exposure) and showed an elevated *R. rickettsii* titre. The patient continued to improve and the symptoms fully resolved.

Case Study 2

Mrs Jones, aged 40, lives in Queensland. She's a farmer / conservation worker / cat breeder. She has not travelled overseas in the last ten years. She thinks she might have been bitten by a tick two years ago. Since around the same time she's been experiencing muscle pain, including joint pain and swelling. She has no signs of a rash now but when she was bitten she had a rash for a while.

Mrs Jones currently finds physical activity difficult and can no longer walk her dog and maintain a full time job. She's seen three doctors in the last two years, who have undertaken a range of musculo-skeletal investigations and ruled out arthritis, occupational overuse syndrome, injuries and rheumatoid arthritis (due to her joint pain), but not been able to give her a diagnosis.

She returns to the GP who reviews her clinical history notes. Since Mrs Jones hasn't been overseas, the GP rules out Lyme disease. The GP notes that Mrs Jones lives in a bushy area with frequent contact with animals, and given her symptoms of lethargy, malaise and muscle pain, suspects tick-borne illness. The GP calls the pathologist and, following advice, requests relevant diagnostic tests for Australian tick-borne disease. When the tests come back negative, and all other disorders are excluded, the GP develops in coordination with Mrs Jones a comprehensive management plan addressing symptom management and improved overall wellness. This includes referring her to other relevant health practitioners as involved in a multidisciplinary care team as required. Referrals may include, for example, psychologists, physiotherapists, or occupational therapists The GP continued to see her regularly for medical assessment of progress and medication management of symptoms.

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APPENDIX B: BIBLIOGRAPHY

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