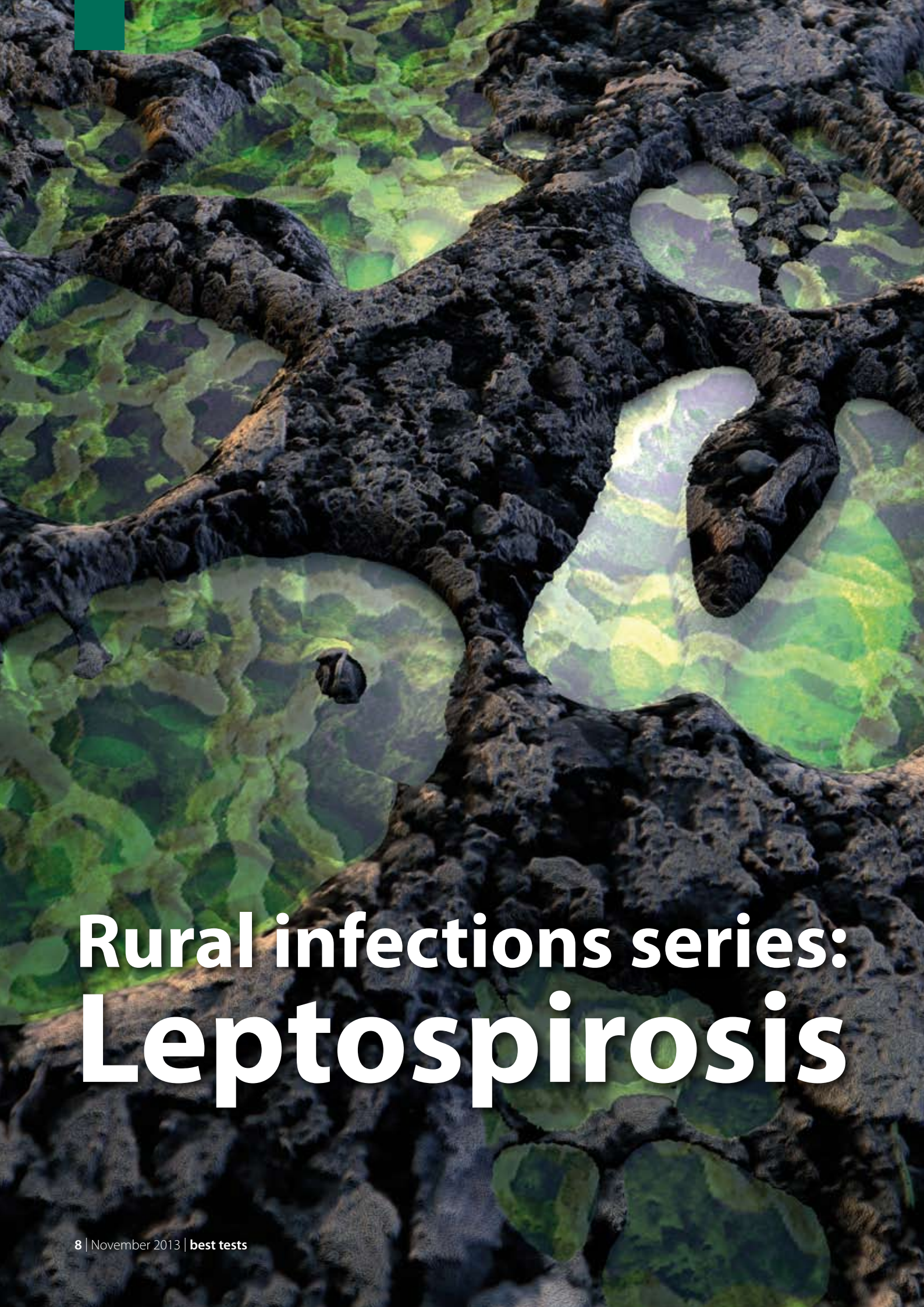
Rural infections series

This article is the first in a series addressing the diagnosis and management of infections that predominantly occur in people who work or live in a rural environment. Most of these infections are caused by bacteria, viruses, fungi or parasites which infect animals but can also pass to humans (known as zoonoses). Examples of rural infections in New Zealand include: leptospirosis, campylobacter (seasonal), giardiasis, orf, cryptosporidium, atypical tuberculosis, rickettsial fever and Q fever.

Most rural infections are rare in the wider New Zealand population and may not be regularly encountered in a typical general practice. Some occur primarily in certain groups or occupations, e.g. leptospirosis in meat processors and farmers. Others have seasonal variations, e.g. campylobacter occurs in urban populations throughout the year, but in spring becomes more prevalent in rural areas as animal handling increases. Some rural infections, such as hydatid parasites, have been successfully eradicated from New Zealand. Others, such as brucellosis, are so rare that they are unlikely to ever be encountered. However, it is important to be aware of all rural infections, as in some instances, they are associated with significant morbidity and potential mortality if not identified early. In addition, reintroduction of infections which have previously been controlled or eradicated could have significant public health and economic consequences.

The rural infections series will cover some of the more common or most clinically significant rural diseases encountered in New Zealand. The first article in this series focuses on the diagnosis, laboratory investigation and management of patients with suspected leptospirosis.



Rural infections series: Leptospirosis

What is leptospirosis?

Leptospirosis is a potentially fatal infectious disease caused by spirochete bacteria of the genus *Leptospira*.[1] It is the most common occupationally-acquired infectious disease in New Zealand, but can be difficult to recognise and diagnose.[2] The incidence of leptospirosis in New Zealand fell considerably from 1980 to 2000,[2] largely due to the introduction of a livestock vaccine for leptospirosis. Incidence has fluctuated since then; the current incidence is 2.5 cases per 100 000 people per year.[3]

Leptospirosis is associated with a broad spectrum of severity, ranging from subclinical infection to severe illness. Typically the infection falls into one of two main clinical syndromes. Most people with leptospirosis will have a self-limiting, influenza-like illness.[4] However, a small proportion of people develop severe illness, often referred to as Weil's disease. This is characterised by jaundice, pulmonary haemorrhage and multiple organ failure.[4] In developed nations, death is rare, but may occur secondary to cardiac arrhythmias, renal failure or pulmonary haemorrhage.[1, 4] At least one confirmed fatal infection has occurred in New Zealand in recent years.[5]

Leptospires pass from mammals, such as rats, dogs, pigs and cattle, to humans across mucous membranes, conjunctivae or broken skin. Infection may occur through direct contact with urine or tissue from infected animals, or indirectly via infected water, damp soil and vegetation.[6, 7] It is rare for human-to-human transmission of leptospirosis to occur.

Because of this mode of transmission, most leptospirosis infections occur in people living or working in an agricultural or rural setting or undertaking recreational activities in these areas. This includes farmers, share milkers, abattoir workers, veterinarians, butchers, drain layers, sewage workers, plumbers, miners, fishermen, hunters, swimmers and trampers. Travellers returning from overseas, particularly from tropical areas, are also at higher risk of exposure to leptospirosis, especially those exposed to certain conditions (e.g. flooding) or activities (e.g. caving or fresh-water sports).

How is leptospirosis diagnosed?

The diagnosis of leptospirosis is usually clinical, with specific laboratory testing used to retrospectively confirm the diagnosis for Notification purposes (see: "Leptospirosis is a Notifiable disease", over page).

Clinical presentation and patient history

The incubation period of leptospirosis varies from 2 – 30 days (mean ten days).[6] The eventual symptomatic illness can range from mild to severe.[8] Approximately 90% of people will have an acute, self-limiting, febrile illness.[8] The remaining 10% will develop a more severe, potentially life-threatening condition.[8] Signs and symptoms of leptospirosis are classically biphasic, although in many severe cases the distinction between the two phases is not apparent.

The initial phase of leptospirosis is an acute-onset febrile illness lasting three to nine days.[8] The most common symptoms are chills or rigors, myalgia, headache and conjunctival suffusion.[4] Conjunctival suffusion is relatively specific to leptospirosis, and typically appears on the third

Leptospirosis is a Notifiable disease

Leptospirosis is a Notifiable disease. Suspected cases should be reported to the local Medical Officer of Health. Investigations should be requested for confirmation of the disease, but it is not necessary to wait for laboratory confirmation before reporting a case.

Confirmation for Notification purposes requires one of the following results:[2]

- Detection of leptospiral nucleic acid from blood, urine or spinal fluid
- A four-fold or greater rise in leptospiral microscopic agglutination titres (MAT) between acute and convalescent sera
- A single agglutination titre of > 400 by MAT
- Isolation of leptospires from blood, urine or spinal fluid

More information on testing can be found in "Investigations", Page 11.

Further information and the required forms for reporting occupational exposures can be found at: **www.business.govt.nz/healthandsafetygroup/notifications-forms/nods**

or fourth day of the illness.[8] It presents as bilateral redness (hyperaemia) and oedema (chemosis) of the conjunctiva, without an inflammatory exudate. An erythematous macular rash, nausea, vomiting and fatigue may also be present, but are less typical features of leptospirosis.[8]

The initial phase is usually (but not always) followed by an asymptomatic period lasting two to three days, before the second (immune) phase begins.[1, 3, 8]

The immune phase occurs as serum IgM antibodies increase and the spirochetes disappear from the blood and cerebrospinal fluid. The response to the antibodies ranges from a more severe form of the initial phase (as above), including aseptic meningitis, to Weil's disease, characterised by jaundice, renal failure, pulmonary symptoms (dyspnoea, chest pain and haemoptysis), myocarditis, cardiac arrhythmias and haemorrhagic diathesis (spontaneous bleeding).[4] In severe infection, multiple organ failure can cause a wide range of symptoms.

Examination

Findings on examination may differ widely among patients. Signs will vary depending on the stage and severity of the illness and the organ systems involved.

A general examination should be performed and will indicate features typical of an infection, such as fever (up to 40°C), tachycardia and muscle tenderness.[8] Localised tenderness in the calf muscles and, in particular, in the paraspinal muscles, is an important, relatively specific finding.[4] Hypotension may be found in patients with severe infection.

A brief eye examination is important for both diagnosis and identification of complications. Photophobia, jaundice and bilateral conjunctival suffusion are often present.[4] Optic neuritis (inflammation of the optic nerve) and uveitis (inflammation of the uvea, including the iris, ciliary body and choroid) can develop as secondary complications.[8]

Palpation of the abdomen may indicate abdominal tenderness and hepatosplenomegaly.[4]

Auscultation of the patient's chest may indicate crackles and wheeze associated with pulmonary oedema. Signs of consolidation, such as bronchial breath sounds, dullness to percussion and reduced chest movement, may be present in severe cases due to pulmonary haemorrhage.

A brief neurological examination should be conducted in patients with suspected leptospirosis with severe signs and symptoms. Aseptic meningitis is suggested by vomiting, headache and meningeal irritation (neck stiffness and photophobia). Immediate referral to hospital is required for anyone presenting with signs and symptoms of suspected meningitis.

Differential diagnosis

The symptoms and signs associated with leptospirosis are non-specific, therefore there are a wide range of other conditions that should be considered in the differential diagnosis, including:[8]

- Influenza
- Other causes of meningitis and meningococcal disease
- Viral hepatitis
- Septicaemia
- HIV seroconversion illness
- Toxoplasmosis
- Other rural infections, e.g. rickettsial infections such as murine typhus (Page 13)
- Tropical diseases, such as yellow fever and malaria; consider in people returning from overseas travel

Investigations

Specific testing for leptospirosis should be used to confirm a suspected diagnosis. However, as the results will not be immediately available (results may take up to three days, or more, depending on the testing laboratory), treatment can be commenced based on the clinical diagnosis.

Serology should be requested first-line for a patient with suspected leptospirosis.[9] Polymerase chain reaction (PCR) testing for DNA should be added if the patient's symptoms are severe or if infection is thought to be acquired through occupational exposure.

N.B. Patients who have laboratory-confirmed leptospirosis due to an occupational exposure are eligible for ACC cover.

Serology is used to retrospectively confirm leptospirosis,[4] and should be requested whenever there is a reasonable suspicion of the infection.[2] Antibodies begin to appear five to seven days after the onset of symptoms,[10] and can remain raised for several months.[7] Two serology samples are required: referred to as the acute and convalescent samples. The first sample should be taken at the initial presentation, with the approximate date of the start of the illness recorded on the form. The second sample should be taken a minimum of 10 – 14 days after the first and ideally at 21 days after the onset of symptoms. A four-fold increase between titre levels in the first and second samples is considered diagnostic of leptospirosis.[10] In some patients, seroconversion is delayed (>30 days), therefore if both samples are negative but there is still a suspicion of leptospirosis, a third serum sample should be requested. Patients with a previous exposure to leptospirosis will often have a positive first sample, but this does not necessarily indicate current infection. An increase in titre levels in the second sample would suggest active infection.

The serology test is specific to the Leptospira genus, but does not differentiate between serovars, i.e. different "strains" of leptospirosis. Positive serology samples are forwarded to Environmental Science & Research (ESR) for microscopic agglutination titres (MAT) which test for antibodies to specific serovars. This information is of limited use for the management of leptospirosis, but is important for epidemiological monitoring.

PCR testing for Leptospira DNA should be requested in addition to serology if the infection is severe, or for confirmation of an occupationally acquired infection, as the results will be available more rapidly than those from paired serology. The type of sample for PCR depends on the duration of the illness: during the first week of signs and symptoms a blood sample should be collected (approximately 5 mL in an EDTA tube; usually purple top). After the first week, a urine sample (at least 20 mL) is used, as leptospires will no longer be reliably detectable in the blood. Due to the intermittent excretion of leptospires in urine, a negative result does not exclude leptospirosis, and a repeat sample may be necessary if there is still a strong clinical suspicion of the infection.

If the patient develops meningitis, a cerebrospinal fluid sample obtained in a secondary care setting can also be used for PCR testing in the first ten days of infection.[10]

Leptospirosis culture is available from some New Zealand laboratories, however, the results usually take a significant time, making it impractical for clinical use.

Other laboratory investigations

Additional laboratory investigations are not necessary for the

diagnosis of leptospirosis. However, some tests may be useful to add evidence to a suspected diagnosis of leptospirosis while waiting for results of leptospirosis-specific testing. Most findings will, however, be non-specific. The following tests may be considered:

- Full blood count – lymphocytopaenia is common in people with leptospirosis.[9] Leukocytes may be low, normal or high, but are commonly associated with a left shift.[8] Thrombocytopaenia is also present in up to 50% of people with leptospirosis.[6]
- LFTs – increases in transaminases, alkaline phosphatase and bilirubin may be seen on liver function tests.[6]
- Serum creatinine – levels may be elevated due to tubular damage and dehydration.[8]
- Urinalysis – proteinuria, pyuria and microscopic haematuria may be present, with granular casts on microscopy.[6]

Managing leptospirosis

It is not necessary to wait for the results from laboratory testing for leptospirosis before starting treatment if there is a strong clinical suspicion of the infection.[1] Discussion with an Infectious Diseases Physician is encouraged in addition to notification to the Medical Officer of Health.

Doxycycline 100 mg, twice daily, for five to seven days is the first-line treatment for leptospirosis in the community setting. Amoxicillin 500 mg, three times daily, for five to seven days is an alternative.[1, 11] Treatment is most effective if antibiotics are initiated within five days of symptom onset, after which the efficacy of antibiotic treatment is less certain.[1, 12] In practice, however, treatment is usually initiated in patients with severe illness regardless of the date of onset.[1]

As with other spirochete infections, e.g. syphilis, antibiotic treatment can be associated with the development of a septicaemia-like reaction in the first few hours after starting treatment, due to the sudden release of endotoxins as the bacteria die.[4] This is referred to as a Jarisch–Herxheimer reaction. This reaction is assumed to be rare, although the exact prevalence in patients with leptospirosis treated with antibiotics is unknown.[13] Patients should be instructed to seek immediate medical attention if they become acutely unwell after starting the course of antibiotics.

When should a patient with leptospirosis be referred?

All patients with severe infection or signs of meningitis should be referred to hospital immediately.[1] Treatment with intravenous antibiotics, e.g. benzylpenicillin 1200 mg IV, every four to six hours, for five to seven days is usually required.[11] Intensive supportive care with particular attention to fluid and electrolyte balance is also often necessary.[1] Further treatment is dependent on complications, e.g. patients who develop acute renal failure may require haemodialysis.[1]

All women who are pregnant and are suspected of having leptospirosis of any severity should be referred to hospital. Leptospiral infection in either early or late pregnancy results in miscarriage or premature delivery in more than 50% of cases.[4]

Consideration should be given to referral to an Infectious Diseases Physician for people with risk factors for developing severe illness. Risk factors include age less than five years or over 65 years and the presence of co-morbidities, such as liver disease or an immunocompromised status.[4]

Preventing future infections

Primary prevention of leptospirosis focuses on educating people to avoid high-risk exposure, such as immersion in fresh water that could be infected, contact with stagnant water and contact with animal urine. However, for many people who are occupationally exposed, avoidance will not be possible. Minimising exposure to animal urine through the use of protective clothing (e.g. gloves, goggles or face shields, gumboots) and good hygiene is recommended. Preventive measures are now widespread in certain industries, such as dairy and meat processing.[5]

Advise patients who have a high level of unavoidable occupational risk to be aware of leptospirosis and its prevention and to present to primary care if they develop flu-like symptoms.

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Murine typhus: an important differential diagnosis

Murine typhus is a flea-borne infection caused by the bacteria *Rickettsia typhi*.[14] Infected fleas are usually carried by rats. In New Zealand it is present in warmer, wetter areas of the North Island, particularly Waikato and Auckland.[9] It is increasingly associated with people who have a rural occupation and/or residence.[9]

Patients with murine typhus present in a similar way to those with leptospirosis, and clinically the two infections are difficult to differentiate. An erythematous macular rash on the trunk is more typical of murine typhus and conjunctival suffusion is more indicative of leptospirosis.[9] A Waikato study found that in people presenting with febrile illness, a low lymphocyte level plus a rural occupation was associated with leptospirosis, whereas a low platelet count (thrombocytopaenia) and a rural residence was associated with murine typhus.[9] However, this would not be sufficient to differentiate between the conditions as leptospirosis can be associated with a low platelet count also.

Serology can be used to differentiate between leptospirosis and murine typhus.[9] It is recommended to also test for murine typhus in patients with suspected leptospirosis who were exposed in areas with higher prevalence of rickettsial infection, e.g. the Waikato. The same sample that has been used for leptospiral serology can be used for rickettsial serology. Indicate on the request form that the laboratory should add rickettsial serology if the leptospiral antibodies are negative.

Patients with murine typhus are managed in the same way as those with leptospirosis; doxycycline is the first-line treatment.[9] Murine typhus is a Notifiable Disease.

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