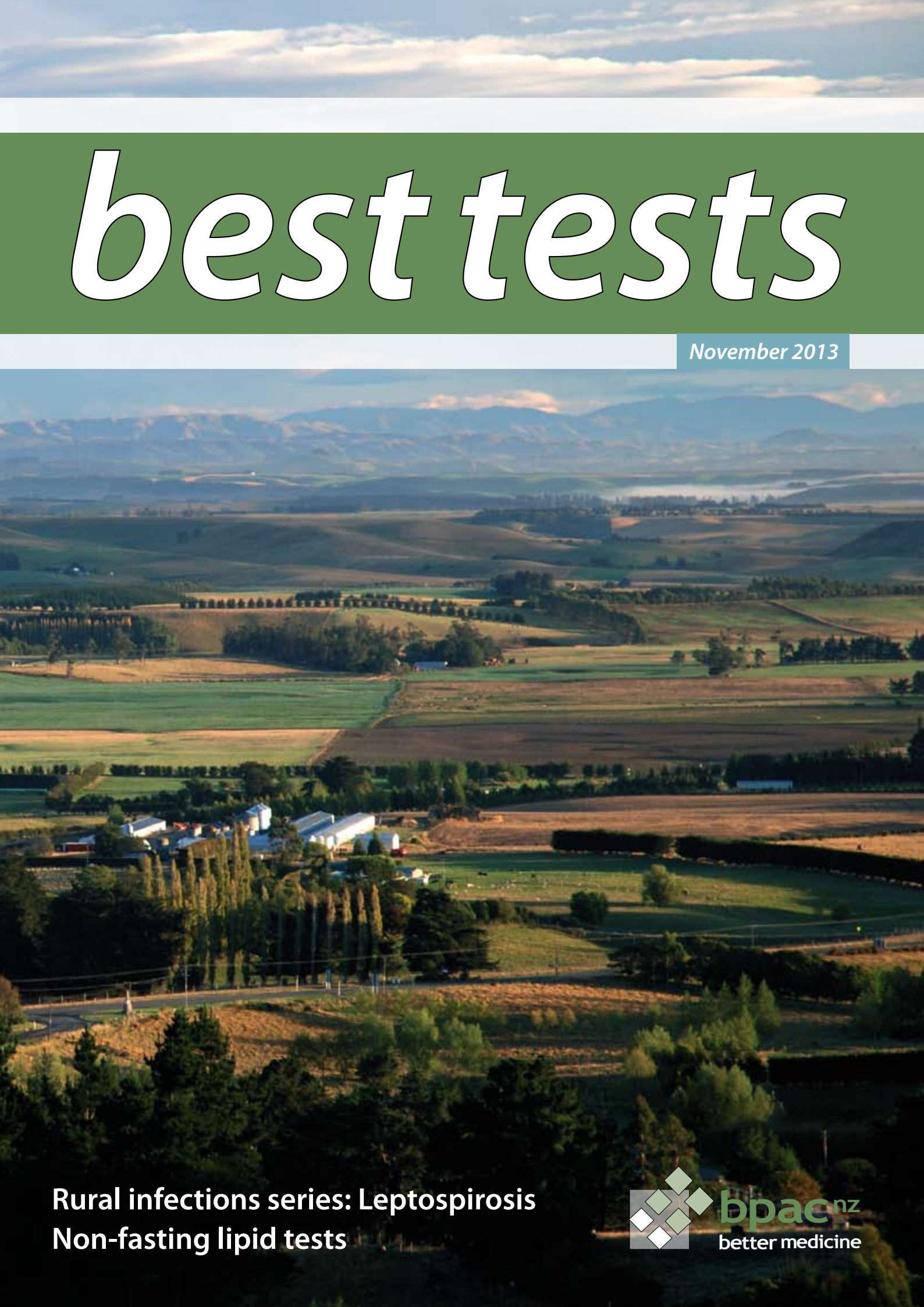
best tests

November 2013



Rural infections series: Leptospirosis
Non-fasting lipid tests

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better medicine

We would like to acknowledge the following people for their guidance and expertise in developing this edition:

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Best Tests is published and owned by bpac^{nz} Ltd

ISSN 2324-304X (Print)
ISSN 2324-3058 (Online)

Bpac^{nz} Ltd is an independent organisation that promotes health care interventions which meet patients' needs and are evidence based, cost effective and suitable for the New Zealand context.

Bpac^{nz} Ltd has five shareholders: Procare Health, South Link Health, General Practice NZ, Pegasus Health and the University of Otago.

Bpac^{nz} Ltd is currently funded through contracts with PHARMAC and DHB Shared Services.

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Contributed by Dr Stephen du Toit.

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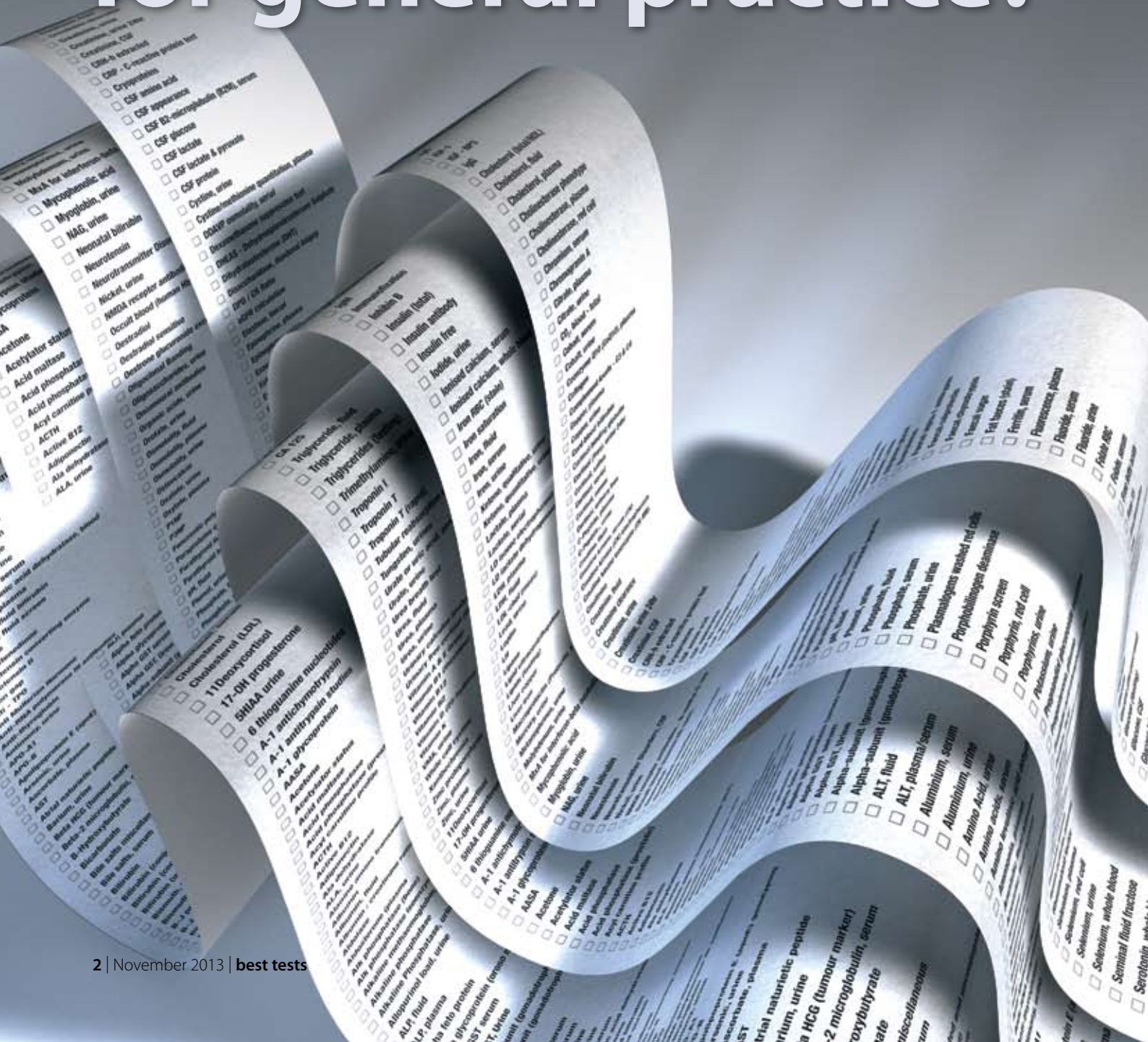


A new schedule for laboratory testing in New Zealand

In October, 2013, a new laboratory test schedule and accompanying referral guidelines were completed and are now available online. It is anticipated that clinicians will become more aware of these guidelines over time as District Health Boards (DHBs) begin to adopt the recommendations.

The project, which involved a review of all publicly funded laboratory tests available in New Zealand, was managed by DHB Shared Services. The schedule and guidance documents were developed by the Laboratory Schedule Review group and several specialist subgroups (see opposite).

The aim of the laboratory schedule review project was to develop a consistent list of tests that are available and funded across DHBs. These tests have been categorised into two groups, termed Tier One and Tier Two (Page 4). Guidelines for the appropriate ordering of selected tests were also developed. Laboratory tests that were regarded as obsolete or clinically inappropriate have been removed, or in some cases superseded with newer tests.

The Laboratory Schedule Test List and Laboratory Test Guidelines are available from:
www.dhbsharedservices.health.nz/Site/Laboratory/Laboratory-Schedule-Review-Project.aspx

Why was the review required?

In the longer term it is expected that the Laboratory Schedule will form the basis of a national test schedule. A key future goal is the integration of the test schedule and referral guidelines into Practice Management Systems in preparation for fully supported electronic test ordering (e-requests). Until that time, the schedule and guidelines are intended to form a framework and to provide recommendations for the appropriate ordering of tests. How the recommendations are implemented at this stage will be determined by individual DHBs. The guideline document aims to provide DHBs with information on which to base local clinical care pathways and funding decisions. While the test guidelines are not intended to take precedence over established local care pathways or other guideline documents, over time they should enable clinical pathways to become more nationally consistent.

Laboratory Schedule Review Group

The Laboratory Schedule Review Group included representatives from primary and secondary care, medical laboratory scientists and clinicians, and specialists and managers from DHBs, with project sponsorship and management from DHB Shared Services.

Laboratory Subgroup Members included specialists in the following fields: microbiology, clinical biochemistry, haematology, immunology, histology, cytology, anatomic pathology and genetics.

Guidance for the ordering of laboratory tests by Midwives was also developed. A separate list of tests that can be ordered by a Midwife is included in the Laboratory Schedule Test List document.

Groups of health care professionals that were not able to be considered during the development of the documents included Nurse Practitioners and community Dietitians, and clinicians who order tests in a hospital setting as part of a specialist team, e.g. House Surgeons, Dietitians and Resident Medical Officers. Management of test ordering by these health care professionals should continue as per current guidelines within each DHB or within the clinician's specialist scope of practice.

The Laboratory Schedule Test List

The Laboratory Schedule Test List categorises tests into general areas, e.g. chemical pathology, haematology, and then further categorises the tests into Tier One and Tier Two tests.

A Tier One test can be ordered by any medical practitioner* with a current practising certificate in New Zealand. Tier One tests include the "core" tests requested frequently in primary care, e.g. full blood count, INR, creatinine and electrolytes, along with many other tests that are only ordered intermittently by General Practitioners.

* A separate list has been developed for midwives (see: "Laboratory Schedule Review Group, previous page).

A Tier Two test is regarded as a specialist test that can only be ordered by a clinician with "appropriate vocational registration or credentialing". It is intended that the ordering of some Tier Two tests is restricted to the specialists named in the schedule, e.g. a request for sex hormone binding globulin (SHBG) should be from an Endocrinologist, O&G specialist or Chemical Pathologist. In practice, however, the "rules" are not intended to be unnecessarily restrictive and any practitioner can order a Tier Two test if they have endorsement or pre-authorisation by a relevant specialist, or if the test falls within their area of expertise. The clinician requesting the test can also consult with a laboratory pathologist for advice and approval for the use of the test.

For some tests in each tier a clinical guideline has been developed to direct appropriate use (see opposite). This is indicated in the comments section of the Laboratory Schedule Test List with the word "Guideline". If there are specific requirements that apply when ordering a test, these are identified within each individual guideline with the words "Referral criteria available". The laboratory may query the test if the reason for requesting it is not within these parameters. Examples of Tier One tests for which a guideline has been developed include growth hormone, amino acids, faecal calprotectin, T3 and T4 and carcinoembryonic antigen (CEA).

Some tests are categorised as both Tier One and Tier Two and also have supporting information to guide appropriate use. In some situations a Tier One test can only be ordered if the referral form contains appropriate clinical information, otherwise the test is regarded as a Tier Two test, and it should be ordered by a specialist as indicated in the schedule. For example, serum cobalt and serum chromium can be ordered by any medical practitioner if the clinical information provided states that this test is being used in a patient with a metal-on-metal joint replacement. If this indication is not specified, then the test is regarded as a Tier Two test and the laboratory may not proceed with the request.

How is the Laboratory Schedule Test List organised?

In the Laboratory Schedule Test List, tests are listed alphabetically, e.g. in the chemical pathology and microbiology test sections, or are listed in relevant subcategories within a specialty, e.g. coagulation tests within the haematology section and allergy tests within the immunology section. Approximately 80% of the tests are in the chemical pathology section.

For each individual test:

- The Tier is indicated
- Specialists who can order the test may be listed for some of the Tier Two tests
- A note in the comments box may indicate if there is a guideline available that restricts or recommends the use of the test, if there are specific referral criteria for the use of the test or if the test is unfunded and there may be a charge to the patient

In addition, the microbiology section has an extra column indicating whether the infection being tested for is Notifiable under the Health Act or the Tuberculosis Act. A number of notes also follow giving more specific advice about notification, e.g. patients with acute hepatitis B and C (including those with neonatal hepatitis B and documented hepatitis C seroconversion within 12 months) should have their condition notified to the Medical Officer of Health. Some microbiology tests include a comment that consultation with a Public Health specialist is indicated. This consultation can fulfil the requirement for specialist advice prior to ordering of tests.

The genetics section of the schedule varies from the other sections because, due to the rapid increase in the number of tests now available, it was recognised that these could not all be itemised. The list of genetic tests therefore includes the most commonly requested tests. The majority of the genetic tests listed are classified as Tier Two tests and in most situations it is anticipated that General Practitioners will not be ordering these tests. It is recommended that advice be sought before any genetic tests are requested. Genetic tests usually require prior written consent from patients. In addition, these tests are often very costly for the laboratory to undertake.

Laboratory Test Referral Guidelines

Referral guidelines have been developed for approximately 50 individual tests on the schedule. These guidelines provide recommendations for the ordering of tests, and for certain tests, referral criteria.

Depending on the individual test, each guideline may include:

- An overview of the place of the test in a clinical setting
- Supporting information explaining why the test is subject to a guideline
- Indications for the test and any referral criteria (this should be included in the clinical information on the request form)
- Specific instructions for collection of the specimen
- Information on the frequency of testing
- Links to further information
- References for the information in the guideline

What impact will the schedule and guidelines have on primary care?

At the present time, clinicians are unlikely to notice a change to their current practice as the majority of tests ordered by primary care clinicians are either Tier One tests, or within the clinician's vocational scope of practice as a Tier Two Test. Almost all of the "day-to-day" tests used in the community, such as a full blood count, CRP and liver function tests are Tier One tests and do not have a guideline or specific referral requirements.

Tests that are Tier Two and do not fall under the scope of practice for the clinician can still be ordered, but this requires prior discussion and approval from a relevant specialist or laboratory Pathologist.

Some unfunded tests are also listed. Generally these are tests where there is a limited body of evidence to support the use of the test or the test has been replaced with either a more accurate or more cost-effective alternative. For example, salivary testosterone is no longer funded due to lack of accuracy and Chlamydia IgG is also not funded because a more appropriate test is available (Chlamydia trachomatis nucleic acid amplification test – NAAT).

Examples from the Schedule and Guideline

C-Reactive Protein (CRP)
This is a Tier One test with no restrictions, referral criteria or guideline attached.

Erythrocyte Sedimentation Rate (ESR)
This is a Tier One test with a guideline that provides recommendations for appropriate use. Many individual laboratories have already produced guidance regarding the appropriate use of ESR, but the new Schedule and Guideline aims to standardise this information.

The ESR guideline provides a brief overview of the limitations of the test in terms of the accuracy of measurement, the influence of physiological variables (other than inflammation) and the role of other factors such as the patient's haemoglobin and plasma protein levels. CRP is recommended as the preferred investigation of disorders due to inflammation or infection.

The conditions included in the guideline, where it is recommended that ESR may have a role, are:

- Systemic lupus erythematosus
- Rheumatoid arthritis
- Kawasaki disease
- Rheumatic fever
- Hodgkin lymphoma
- Temporal arteritis (giant cell arteritis)
- Inflammatory bowel disease in children (initial assessment)

If the patient is suspected to have a plasma cell dyscrasia, ESR, although not restricted, is not recommended as a "screen" - the appropriate initial test is protein electrophoresis (which may be followed by serum free light chains).

Vitamin D
Vitamin D is an example of a test that is regularly used in primary care but is not strongly supported by evidence. Under the new Laboratory Schedule, vitamin D is categorised as both a Tier One and a Tier Two test, and also has an accompanying guideline.

General Practitioners can request the test, but only when following the vitamin D guideline. The guideline outlines

the limited indications for which the test can be requested by a General Practitioner. The specific indication must be clearly specified on the request form. The requirements are that the person must be at high-risk of vitamin D or calcium abnormalities, for example:

- Patients with rickets or osteomalacia, known osteoporosis, abnormalities of calcium/phosphate metabolism or a raised ALP with a likely bone origin
- Patients with cystic fibrosis, those who require a special diet (e.g. PKU), patients with a renal transplant or those taking anticonvulsant medicines
- Children aged under 16 years, refugees, and patients prior to treatment with bisphosphonates for osteoporosis, or interferon for hepatitis C

As a Tier Two test, vitamin D may be ordered by an Endocrinologist, Hepatologist, Rheumatologist, Nephrologist, Gastroenterologist or Gastrointestinal Surgeon. However, General Practitioners or any other relevant specialist, may also order the test with pre-authorisation from any of the specialists listed or a Chemical Pathologist.

Insulin (total)

Total insulin is categorised as both a Tier One and Tier Two test and a guideline has been developed for the test. As a Tier One test, total insulin can only be requested by General Practitioners for a patient following bariatric surgery in order to investigate hypoglycaemia. This indication and the patient's relevant clinical information should be included on the request form.

As a Tier Two test, total insulin may be ordered by a Paediatrician, Endocrinologist, Hepatologist or Gastrointestinal Surgeon. General Practitioners can still request the test provided they have prior authorisation from these specialists or a Chemical Pathologist.

Insulin can be an important test when used in the investigation of hypoglycaemia, particularly if an insulinoma or islet cell hyperplasia is suspected, however, investigation of a patient in this clinical situation would normally be carried out in conjunction with an Endocrinologist. A plasma glucose test should also be simultaneously collected to allow correct interpretation of the results. In addition, the guideline states that fasting insulin is not recommended for assessing insulin resistance, although experts continue to debate the clinical usefulness of doing so.

Catecholamines (urine)

Testing for catecholamines in the urine is categorised as a Tier Two test. While phaeochromocytoma is a rare but important cause of secondary hypertension to consider in some patients, the most sensitive and specific first-line test is urine or plasma metanephrines, both Tier One tests. The decision on which of these tests to use will depend in part on local availability. Catecholamines should only be requested in specific and limited circumstances, such as in a patient where there is suspicion of neuroblastoma or malignant phaeochromocytoma. Investigation of these conditions would normally be done in consultation with a relevant specialist in a hospital setting.

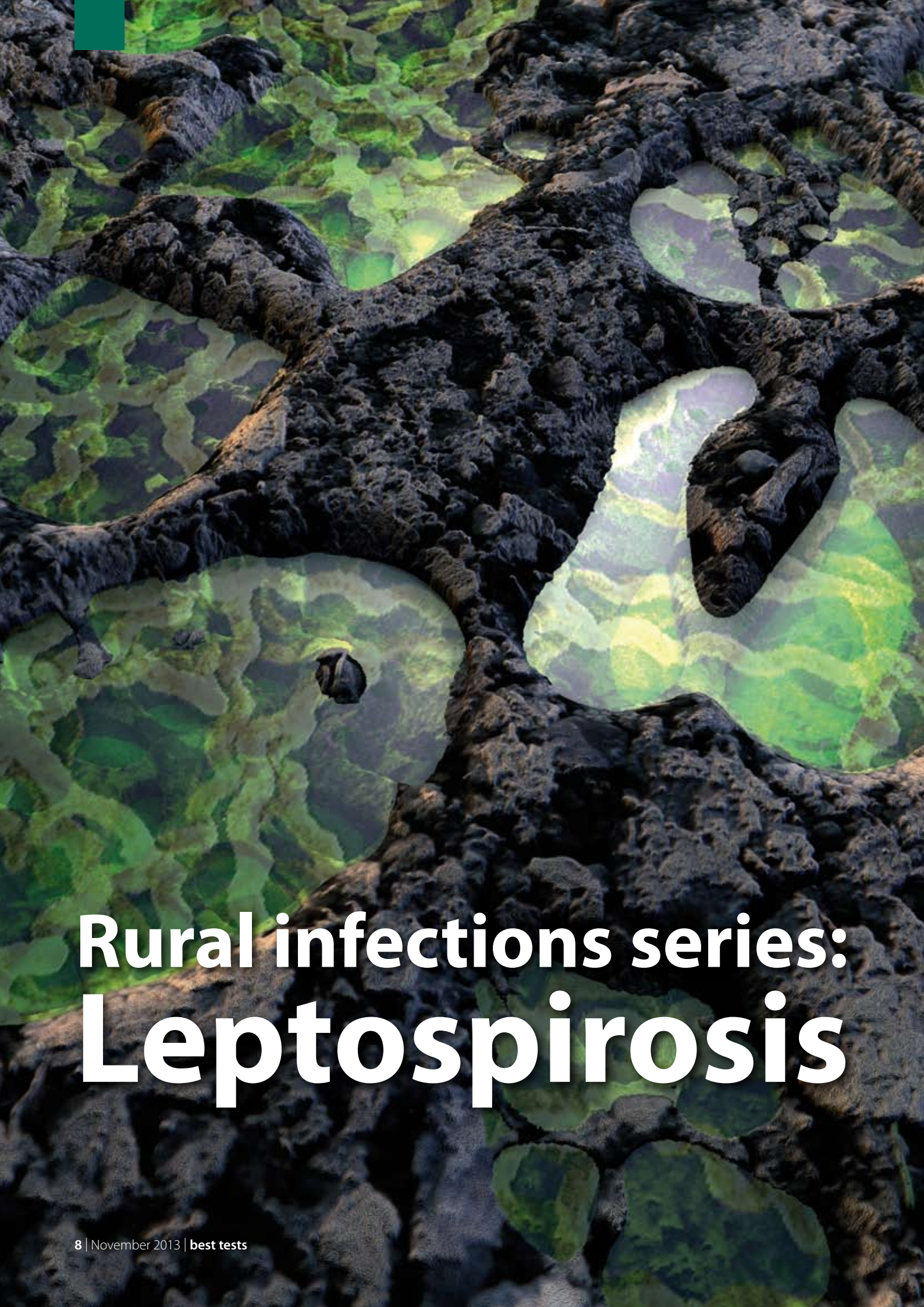
ACKNOWLEDGEMENT Thank you to **Robyn Blue**, Laboratory Schedule Review Project Manager, DHB Shared Services, **Dr Rosemary Ikram**, Clinical Microbiologist, Chair of Microbiology Subgroup and **Dr Cam Kyle**, Clinical Biochemist, Co-Chair of Clinical Biochemistry Subgroup for expert review of this article.

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.

ACKNOWLEDGEMENT Thank you to **Dr Susan Taylor**, Clinical Microbiologist, Middlemore Hospital, Counties Manukau DHB and **Dr Rosemary Ikram**, Clinical Microbiologist, Christchurch for expert review of this article.

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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"Oh and while you are here..."

Fasting may be unnecessary for lipid testing

A growing body of evidence and expert opinion suggests that fasting is not necessary prior to a lipid test in most scenarios. Exceptions to this include initial investigations in people with familial hyperlipidaemia and monitoring response to treatment in patients with high triglyceride levels. The advantage of non-fasting testing is that it is likely to result in more patients being tested, including those who are "hard to reach", and therefore greater identification of patients at high cardiovascular risk. Non-fasting lipid test results have been shown to have only small variations compared to fasting samples, and a non-fasting result can be used reliably to calculate cardiovascular risk.

Fasting for at least eight hours prior to a lipid test has been standard practice in New Zealand and internationally for many years. However, a growing body of evidence and international expert opinion suggests that a non-fasting lipid profile can be used in most situations. This includes:[1–4]

- Calculating cardiovascular risk
- Testing for hyperlipidaemia
- Monitoring response to statin treatment

At present, the majority of guidelines recommend a fasting serum lipid test. This recommendation is based on achieving consistency between patients and over multiple tests by ensuring a relatively standardised metabolic state. It is also because the majority of research has been performed using fasting lipids, therefore it was assumed that making comparisons and analysing risk would be less precise if using non-fasting tests.[1]

Fasting requirements, however, are difficult for some patients and can reduce adherence with testing requests, delay results and place strain on testing facilities as a large influx of patients present for testing each morning. In addition, a fasting sample does not reflect the true biological state in which people spend the majority of their time.[2, 5]

There is little difference between fasting and non-fasting results

Fasting does not greatly alter the levels of lipid parameters.[5] Large-scale studies have indicated that mean lipid levels varied between fasting and non-fasting samples by:[1, 3, 5]

- Less than 2% for total cholesterol (approximately 0.2 mmol/L decrease for non-fasting vs fasting)
- Less than 2% for high-density lipoprotein (HDL) cholesterol (approximately 0.1 mmol/L decrease for non-fasting vs fasting)
- Less than 10% for calculated low-density lipoprotein (LDL) cholesterol (approximately 0.2 mmol/L decrease for non-fasting vs fasting)
- Less than 20% for triglycerides (approximately 0.3 mmol/L increase for non-fasting vs fasting)

Overall, given that clinically important reductions in total and LDL cholesterol are considered to be greater than 1 mmol/L, the clinical significance of this variation will often be negligible.[3] These variations in lipid parameters are derived from average values in large population studies and deviations may be greater in individual patients. However, the differences are well within average biological variation between patients for each parameter.[6]

Food intake has a minimal effect on lipid levels

A decrease in total cholesterol, HDL and LDL is observed for up to four hours after a standard meal.* [3] A decrease in lipid levels after a meal is perhaps converse to what would be expected, but this occurs due to the dilutionary effect of water contained in the food.[3]

Triglyceride levels are increased for six to eight hours after a standard meal.[1, 3] If a patient has consumed a very high fat content meal prior to testing, or if they have slow lipid particle clearance after food (post-prandial dyslipidaemia), triglyceride levels could be increased more than the estimated 0.3 mmol/L variance, and misrepresent clinical significance.

Measuring non-fasting triglyceride levels may provide additional information for determining cardiovascular risk. Peak non-fasting triglyceride levels, four hours after a meal, are reported to be a strong predictor of cardiovascular events and insulin resistance, and risk equations may be developed based on these levels in the future.[1, 3]

* A "standard meal" is not precisely defined in the literature but can be assumed to be an average sized, main meal, which contains balanced proportions of carbohydrates, protein and fat.

Alcohol can affect both fasting and non-fasting lipid tests

Light to moderate drinking, e.g. one to three standard drinks per day for males or one to two standard drinks per day for females, has very little acute effect on triglyceride levels.[7] However, excessive alcohol intake may cause an increase in triglyceride levels immediately following intake and after fasting.[7] When alcohol consumption is accompanied by a meal containing fat it has a significant additive effect on the resultant triglyceride increase.[7]

When can a non-fasting lipid sample be used?

In general, a non-fasting lipid test would be appropriate in the following clinical scenarios:

- CVD risk assessment
- Initial investigation of lipid levels (unless the patient has a history of familial hyperlipidaemia)
- Monitoring lipid levels over time
- Monitoring response to lipid-lowering treatment (unless the patient has high triglycerides)
- Testing for any reason in patients who are "hard to reach" or have low motivation for undergoing a fasting test

Cardiovascular risk assessment

A non-fasting lipid test is acceptable for most patients requiring a CVD risk assessment.[3, 8] While current guidelines recommend a fasting lipid sample,[9] the benefits of evaluating risk with a non-fasting test in patients who find performing a fasting test difficult, may outweigh any minor differences in overall cardiovascular risk.

Most evidence on calculating cardiovascular risk is based on fasting lipid test results, however, results from non-fasting lipid tests have also been shown to be strongly predictive of adverse cardiovascular events.[1–3] A large meta-analysis of 68 prospective studies, involving over 300 000 patients, concluded that there was no difference in the power of CVD risk prediction in the 20 studies using non-fasting lipid tests, compared to the 48 studies using fasting lipid tests.[8]

During a CVD risk assessment, specific values are entered into a risk calculator, such as the Framingham equation. The Framingham equation uses total and HDL cholesterol values, which have the lowest variation between fasting and non-fasting samples, and a range of other factors, such as blood pressure, to calculate risk.[3] The extra precision gained from

a fasting result is therefore unnecessary.[3] Patients with a low cardiovascular risk and a non-fasting lipid-profile within the ideal range will not require further testing for five to ten years, provided there are no significant changes to lifestyle or diet, or no significant new information arises, e.g. significant family history or relevant new personal history.

Investigating and monitoring hyperlipidaemia

A non-fasting lipid test can be used as an initial investigation of hyperlipidaemia. A non-fasting sample is appropriate for subsequent tests, unless very high triglycerides have been identified (> 4.5 mmol/L, see below).[1, 2]

The initiation of lipid-lowering treatment, e.g. a statin, is based on CVD risk, which can be calculated using a non-fasting sample. A non-fasting lipid test can also be used to monitor response to treatment (unless high triglycerides are being treated).[5] Lowering of LDL is currently the primary indicator of lipid management. A clinically significant change to LDL following statin treatment is approximately 1 mmol/L, therefore variation in LDL levels of 0.2 mmol/L between fasting and non-fasting tests has little clinical importance.[3]

When should a fasting lipid sample be used?

In general, a fasting lipid test should be requested in the following clinical scenarios:

- Initial investigation of lipid levels in patients with familial hyperlipidaemia
- Initial investigation of lipid levels in patients with suspected high cardiovascular risk, who have never had a lipid test before
- Monitoring response to lipid-lowering treatment in patients with high triglyceride levels (> 4.5 mmol/L)

Some clinicians may prefer to initially request a fasting lipid sample in patients who they suspect have a high CVD risk, or familial hyperlipidaemia, and have never had their lipids checked before. This allows a more standardised measure of triglyceride levels, and a bench-mark to be set for comparison.

Non-fasting lipids may then be requested for subsequent CVD risk assessments. However, patients with high triglyceride levels (> 4.5 mmol/L) should be followed up with a fasting test, to improve the accuracy of the calculated LDL results.[1, 2]

When triglycerides are > 4.5 mmol/L a fasting lipid test is preferable for monitoring response to treatment as it provides better standardisation and measurement of the intervention (as triglycerides are more affected by food). The Freidewald equation, which is used to calculate LDL cholesterol, underestimates LDL by approximately 0.5 mmol/L when triglyceride levels rise above 2.5 mmol/L. When the patient's triglyceride level (fasting or non-fasting) is over 4.5 mmol/L, LDL cannot be reliably calculated. A direct measure of LDL can be arranged in such circumstances from most community laboratories (this is not measured as part of the standard lipid panel in New Zealand).

ACKNOWLEDGEMENT Thank you to **Dr Cam Kyle**, Clinical Director of Biochemistry, Diagnostic Medlab, Auckland, for expert review of this article.

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Laboratory investigation of

Exposure to metals or other hazardous substances in the environment

On occasion, General Practitioners will encounter a patient with a concern relating to possible exposure to a hazardous substance. These presentations can be very challenging – the symptoms may be non-specific, there may be no objective evidence of exposure, and the number of potential hazardous substances that the patient has been exposed to may be large. In this situation, laboratory investigation requires careful consideration. Testing is usually only useful if there is evidence of systemic toxicity, and a specific treatment option is available.

Contributed by Dr Stephen du Toit

If a patient presents with a possible exposure to a hazardous substance, what do you do?

Ask the patient if they have a suspicion as to the identity of the hazardous substance, the time and date of suspected exposure and any relevant occupational details if the exposure occurred during work.

Take a history and examine the patient. Assess blood pressure, pulse rate, respiratory rate, temperature, neurological status and presence of gastrointestinal disturbance, such as diarrhoea or vomiting.

As a subset of hazardous substances, diagnosing environmental metal toxicity can be difficult since symptoms and signs are usually non-specific. Diagnosis of metal toxicity generally requires three features to be present:

- A realistic source of exposure
- Symptoms and signs typical of exposure to the metal
- "Abnormal" levels of the metal in an appropriate biological sample

Metal toxicity should be considered in patients with:

- History of exposure
- Unexplained renal disease
- Symmetrical peripheral neuropathy
- Unexplained acute changes in mental/neurological function
- Acute inflammation of nasal or laryngeal epithelium

Examples of conditions that may be caused by metal toxicity include bilateral pain radiating from the feet to the leg with arsenic exposure, renal disease in spray painters with cadmium exposure and early onset of Parkinsonism (age < 50 years) with manganese exposure.

Who can you call?

If the patient has signs of acute toxicity or their history suggests significant and recent exposure, it is recommended to seek advice on management.

Options to consider include the National Poisons Centre (0800 POISON), the TOXINZ database (**www.toxinz.com** – requires a subscription), a Chemical Pathologist or the local district health board's Toxicologist.

Advice from these experts should include treatment options (if any) and collection of samples such as urine or blood to be stored for possible analysis.

What laboratory investigations are appropriate?

Testing for possible chemical exposure requires careful consideration. In general, testing is only useful if there is evidence of systemic toxicity, and a specific treatment option is available. In some situations baseline levels may be helpful and serial tests may also be required. Expert advice is strongly recommended prior to undertaking any testing. It is also recommended to contact the local laboratory to discuss collection of appropriate samples.

There is no single analytical technique that can identify all hazardous substances. Targeted testing (if available) can be used when attempting to identify a specific chemical, e.g. investigating lead toxicity (see: "Lead exposure").

Interpretation of blood and urine tests for chemicals can be complex. Laboratories use inductively coupled plasma mass

Lead exposure

Investigating lead level in a patient with exposure to lead, (e.g. lead-based paint) is an example of an appropriate targeted test.

Guidelines for managing exposure to lead are available from the Ministry of Health. The Medical Officer of Health should be notified of patients with blood lead levels ≥ 0.48 micromol/L. Children with a blood lead level ≥ 0.96 micromol/L and adults with a blood lead level ≥ 3.4 micromol/L should be referred to an appropriate specialist.[2] Patients with elevated lead levels should reduce (or eliminate if possible) exposure to lead and then be re-tested after six weeks and six months.

For further information see: "The environmental case management of lead-exposed persons", available from: **www.health.govt.nz**

spectrometry (ICP-MS) to determine levels of elements in blood or urine, but the analytic process involves "standardising" all ionic states to a single catatonic charge, which can mask toxicity.[1] For some metals, toxicity varies depending on the ionic state. For example, Hg (elemental mercury) is non-toxic, Hg^{2+} (mercury ions) is toxic and CH_3Hg (methyl mercury) is very toxic. Similarly, Cr^{6+} (chromium) is toxic but when it enters cells it is converted to Cr^{3+} which is non-toxic. Biological monitoring using ICP-MS cannot distinguish between toxic or non-toxic forms of chromium, so measuring the source of the possible exposure is more reliable.

What about other types of "toxicity testing"?

Performing wide-ranging screening tests (e.g. hair analysis – see sidebar) for any form of hazardous substance is seldom appropriate. The implications of a positive result need to be considered before a test is requested. All people are exposed to hazardous substances in the environment, and may have detectable levels without being "poisoned". In a normal reference interval, 5% of healthy patients will have results falling outside this range. An "abnormal" result may occur purely by chance, but may cause unnecessary concern. In addition, using population-based reference intervals established overseas may not be appropriate for people in New Zealand.

Tests requested (usually by the patient themselves) from overseas laboratories are particularly difficult to interpret and may result in over-diagnosis and unjustified concern, as well as incurring significant cost to the patient.

Hair analysis is not recommended

Hair analysis is valuable in forensic medicine when assessing acute toxicity, and in drug testing. Hair grows at a rate of 1.06 cm/month, therefore providing a timeline of exposure. While it seems reasonable to expect that hair analysis, using sophisticated modern analysers such as ICP-MS will be useful in assessing long-term exposure to toxic metals, this is not the case.[3]

There are several reasons for this:

- There are no international hair standards available to calibrate the analysers
- Analysis of the same sample by different laboratories yields different results
- Reference intervals are often calculated by using data obtained from testing the samples received. Ideally, reference intervals should be established using samples from healthy individuals. Since reference intervals are not well defined, more (or less) than the arbitrary 5% of healthy, non-exposed patients will have results that fall outside reference intervals.
- The probability of having at least one "abnormal" result increases with the number of tests performed. A large number of analytes (e.g. 20 – 40) are usually tested; the probably of at least one "abnormal" result is 65% for 20 tests and 87% for 40 tests, assuming the reference intervals include 95% of results obtained from healthy individuals[4]
- Patients are constantly being exposed to hazardous substances and hair will always contain some toxic elements
- Hair is exposed to the environment, and in general it is not possible to remove only external contaminants from hair. For example, arsenic deposits on the outside of the hair shaft with exposure to the environment (e.g. washing hair with arsenic-containing water). Arsenic is also deposited on the outside of the hair shaft when arsenic-containing water is ingested.

More research is required to define the correlation between the clinical state, hair analysis and blood test results.[4]

Do exposures to hazardous substances need to be reported?

By law, medical practitioners must inform the local Medical Officer of Health of patients with the following conditions:

- Lead absorption ≥ 0.48 micromol/L (Health Act 1956)
- Poisoning arising from chemical contamination of the environment (Health Act 1956)
- Hazardous substances disease and injury (Hazardous Substances and New Organisms Act 1996).

A hazardous substance is officially defined as anything that can explode, catch fire, oxidise, corrode, or be toxic to humans.

Electronic notifications of hazardous substance exposures (including lead exposures) may now be made through the *bestpractice* Decision Support module, introduced nationwide in 2013. These notifications are assessed by the Medical Officer of Health and Public health unit staff to determine if further follow-up with the patient is required.

Where the diagnosis of poisoning is unclear, discussion with the Medical Officer of Health may assist in deciding if notification is appropriate, what action might be taken, and what if any public health investigation is required.

ACKNOWLEDGEMENT Thank you to **Dr Stephen du Toit**, Chemical Pathologist, Hamilton for contributing this article.

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Hazardous Substances

Hazardous Substances Disease & Injury Notification

GPs in all regions of New Zealand are now able to use e-notification to inform your Medical Officer of Health about hazardous substances, diseases and injuries.

By law, injuries from hazardous substances, lead absorption and poisoning arising from chemical contamination of the environment (including from agrichemical spraydrift) are required to be notified.

Look for 'Hazardous Substances & Lead Notifications' on the Module list of your BPAC dashboard.

For more information on these notifications see the article on page 34 of the April **Best Practice** journal http://www.bpac.org.nz/BPJ/2013/April/docs/BPJ52.pdf.

If you have any questions regarding a patient or notification, please contact your local public health unit.

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