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Rural infections series: Infectious diarrhoea

New Zealand Laboratory Schedule: Biochemistry

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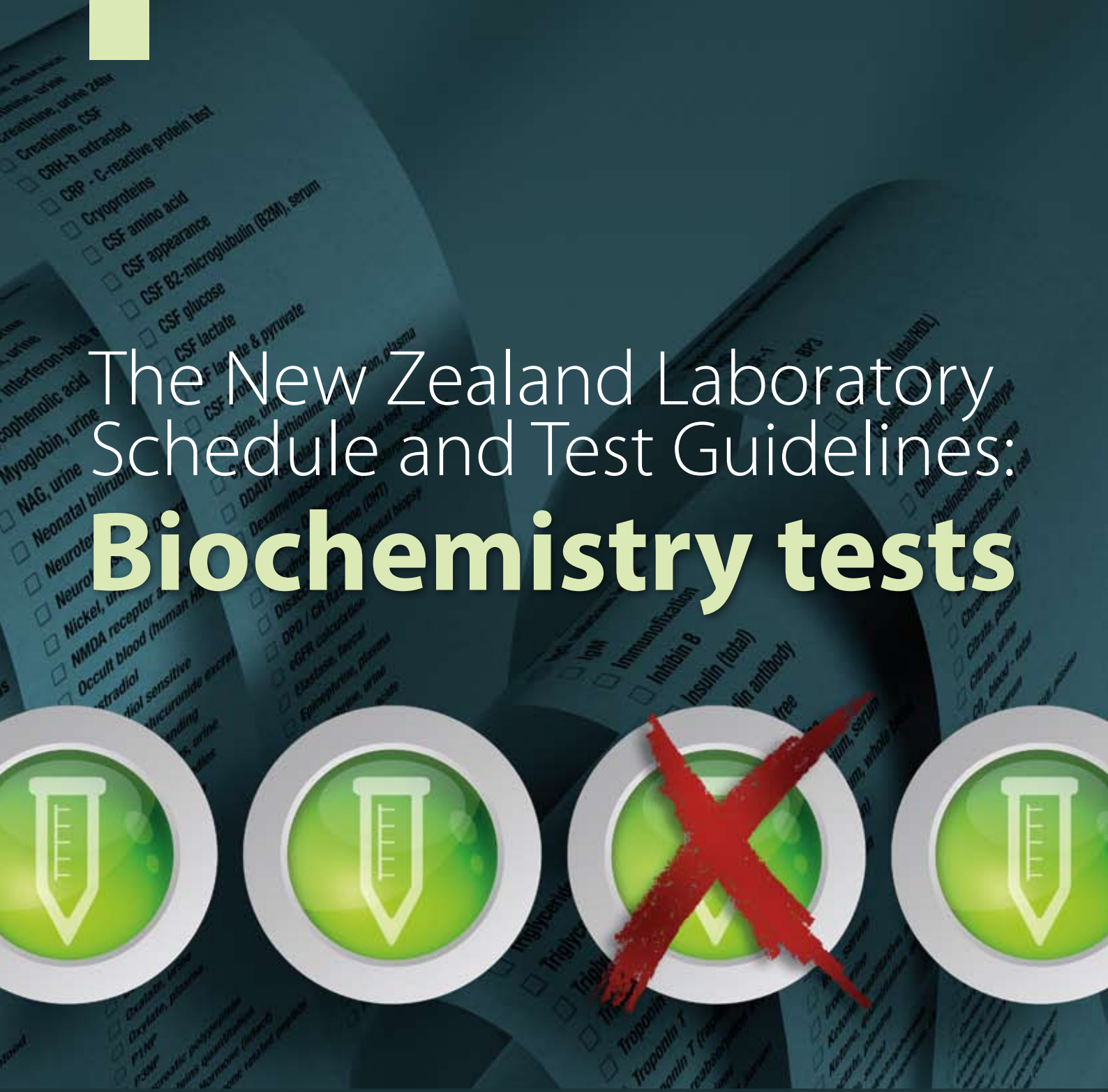

A new laboratory test schedule and accompanying referral guidelines have been developed for health care professionals in New Zealand. The Schedule and Guidelines were released to District Health Boards (DHBs) in October, 2013 and are also available online. The aim was to develop a consistent list of tests that are available and funded across DHBs. An article in Best Tests, Nov, 2013, introduced the new Test Schedule and explained how they have been developed. Tests have been categorised into general areas and then grouped depending on whether they are recommended as a test that can be ordered by any medical practitioner (Tier 1) or whether the test is restricted to specific clinicians (Tier 2). In this article **Dr Cam Kyle** and colleagues discuss the biochemistry tests grouping, and explain why some tests are restricted, why others are now outdated or lack evidence and some tests which are underutilised.

The Biochemistry Subgroup

As part of the wider review of the New Zealand Laboratory schedule, a biochemistry subgroup was formed to identify tests where special expertise was considered appropriate for interpretation of results, and tests where guidelines or restrictions on requesting were thought to be necessary. The group was also asked to identify tests which were outdated or of no clinical value and for which funding should be withdrawn, as well as to identify underutilised tests which should be encouraged first-line.

The key drivers for this process were:

- The desire for a national schedule that was relevant to the current evidence base and best practice
- The desire to develop more consistency of testing across DHBs
- A lack of clarity regarding appropriate and cost-effective testing, as there was no guidance on limiting testing
- The intention for the schedule to interface with an e-labs initiative, and electronic test requesting

Ultimately there was concern not only because of the increasing volume of laboratory testing in general, but also because the requesting of certain "vogue" tests had increased dramatically in a way not justified by current overall evidence. Particular attention was suggested for those tests which "create issues in terms of volume and requesting appropriateness". The background rationale was to allow appropriate, evidence-based spending on pathology testing by DHBs facing increasingly constrained laboratory budgets. The intention of the review was not to place blanket restrictions on tests, but rather to provide guidance on appropriate test requesting.

The guidelines produced are not mandatory but were developed as a resource for individual DHBs to use. They are not intended to replace well-established local protocols or clinical pathways, but rather to support them where judged appropriate by local clinicians and policy setters.

Composition and process of the biochemistry subgroup

The biochemistry subgroup was composed of six Chemical Pathologists representing different DHBs, from both public/academic and private (community) backgrounds, along with a convener from DHB Shared Services. Individual members were each allocated a range of tests to evaluate and present recommendations for wider discussion among the group. Specialists from related clinical disciplines were consulted when appropriate. In all cases where guidelines or restrictions were put in place the strength of evidence base, and the opinions of local experts were considered, and there was ultimately unanimous agreement among the group. Third party stakeholders also had the opportunity to provide feedback on an initial draft set of guidelines, and suggestions were incorporated into the final document.

In biochemistry there were a significant number of "esoteric" tests identified, which were considered to be Tier 2 tests, i.e. requiring special expertise in interpretation. Many of these tests are rarely requested and, while detailed criteria or guidelines for requesting them have not yet been recommended, requestors are encouraged to contact the laboratory or a specialist in the relevant clinical discipline to discuss appropriate requesting and interpretation.

It is intended that the Laboratory Schedule and Test Guidelines will be updated and modified as new evidence comes to light, new tests are added and others become outdated. As electronic ordering becomes standard practice there will be opportunity to guide testing based on clinical presentation and minimise inappropriate testing frequency, e.g. requesting HbA_{1c} more often than every three months without special circumstances.

Biochemistry tests (referred to as chemical pathology in the schedule) were divided into four groups:

A) Tests where it is appropriate to recommend ordering restrictions and/or criteria for funding based on clinical circumstances and/or expertise of referrer

B) Tests which are outdated and which should be funded only in very limited circumstances

C) Tests where public funding was not considered justified based on current evidence

D) Tests which were considered underutilised, but for which requesting guidelines were appropriate to optimise clinical utility

Tests with restrictions

The following tests are examples of those that have recommended guidelines or criteria for their use and should be requested only in specific clinical situations.

Androgen tests

Restricted tests include androstenedione (ASD), dehydroepiandrosterone sulphate (DHEAS), sex hormone binding globulin (SHBG) and free testosterone:

- In the assessment of hirsutism measurement of ASD and DHEAS is not justified unless testosterone is also elevated (except when requested by specialist Endocrinologists, or pre-authorised by a Chemical Pathologist)
- Measurement of sex hormone binding globulin (SHBG) and calculated free testosterone is not justified unless the initial total testosterone result is in a range where SHBG/free testosterone is likely to provide additional clinical value
- Measurement of dihydrotestosterone is only justified in isolated rare clinical scenarios of defective androgen action or response, e.g. partial or complete androgen insensitivity

DHEAS and **ASD** are androgens sometimes measured in addition to testosterone in the assessment of women with hirsutism and possible polycystic ovary syndrome (PCOS). Free testosterone, derived from measurement of total testosterone and SHBG, is also sometimes advocated as providing a better measure of tissue androgen exposure.

The added value of measuring these hormones is very limited in the large majority of patients being evaluated for possible PCOS. The main reason for initially performing such tests is to exclude other secondary causes, particularly virilising ovarian or adrenal tumours. However, these conditions occur very rarely and patients will virtually always have an unusual clinical presentation with relatively severe and rapidly progressive hirsutism, and/or evidence of virilisation. Even for these patients, it is extremely uncommon for there to be isolated elevation of DHEAS or ASD without testosterone elevation (which is usually marked).

N.B. Testosterone levels are not always raised in females with PCOS. Measurement of testosterone levels (total testosterone), while often carried out, is not required for diagnosing PCOS. The diagnosis is based on a constellation of findings related to clinical and/or biochemical evidence of androgen excess, menstrual irregularity and ovarian dysmorphology (usually multiple peripheral ovarian cysts).

Exclusion of other secondary causes such as Cushing's syndrome and congenital adrenal hyperplasia (mostly late onset 21 hydroxylase deficiency) involves measurement of other specific tests (urine free cortisol and/or overnight dexamethasone suppression, and 17OH-progesterone).

Measurement of DHEA or ASD has also been advocated in patients taking these as supplements. However, the biochemistry subgroup consider supplementation with DHEA or ASD ("andro") to be of unproven clinical value (and unclear long-term clinical risk), except in certain situations, such as in patients with premature ovarian failure, hypopituitarism and possibly some other limited settings, such as some female patients with SLE.[1] Even in these patients, measurement of DHEAS and ASD is of unclear and unproven value in monitoring their treatment.

Sex hormone binding globulin (SHBG), which is used to calculate free testosterone, is also of limited value in most patients. Evaluation at LabPlus shows that all female patients with a testosterone > 5 nmol/L will also have a raised free testosterone, and those with total testosterone < 1.3 nmol/L have a free testosterone within reference limits. There is little additional clinical value therefore in measuring SHBG/free testosterone for samples with total testosterone outside these limits. Even for patients with total testosterone within this range, only those with unusually high (e.g. taking oral contraceptives, hyperthyroidism) or low (e.g. obese, insulin resistant) SHBG levels are likely to have a reclassification of testosterone to within or above reference limits based on their free testosterone result. For similar reasons, in males, free testosterone adds value only if the total testosterone is between 7 – 15 nmol/L.

Dihydrotestosterone measurement is extremely expensive and adds little to the clinical management of patients with hirsutism (even those taking 5-alpha-reductase blockers, such as finasteride). This test is of established clinical utility only in patients being evaluated for very rare defects in androgen action or response (e.g. partial or complete androgen insensitivity) in specialist settings.

For further information see: "Reproductive hormones: the right test, at the right time, for the right patient", Best Tests (Feb, 2013).

Tests of adrenal function

24h urine free cortisol (UFC) has well-established value in the initial evaluation of patients with possible Cushing's syndrome.[2] A 24 hour urinary excretion result over four times the upper reference value makes Cushing's highly likely. Lesser degrees of elevation can reflect a broad range of other factors, such as stress, illness, insomnia, depression, anorexia and alcoholism, as well as Cushing's.

The clinical utility of 24h cortisol excretion for the evaluation of possible primary or secondary hypoadrenalism is, however, very limited and the group did not consider this to be an appropriate clinical indication for this test. There are other established means with much better clinical utility to make this diagnosis, such as synacthen testing and, for primary adrenal disease, plasma adrenocorticotropic hormone (ACTH).

While there is a loose correlation between 24h urine cortisol production and cortisol output, excretion can be affected by a range of factors and can vary significantly from day-to-day, even in healthy patients exposed to temporary physical or psychological stress. Patients with primary adrenal insufficiency may also have daily excretion well within reference limits, but output is stimulated by increased ACTH stimulation (in a similar way to patients with mild hypothyroidism with free T4 maintained within reference limits by increased TSH).

Many requests for UFC are made in the belief that functional adrenal insufficiency ("adrenal fatigue") is a cause for chronic fatigue syndrome. There is no substantive evidence for "adrenal fatigue" as a real clinical entity. The use of hydrocortisone treatment in chronic fatigue syndrome is not supported by randomised controlled trial evidence,[3, 4] and both United Kingdom and Australasian guidelines specifically state that hydrocortisone should not be used in chronic fatigue syndrome.[5, 6]

Cortisol binding globulin (CBG) measurement is considered to have no clinical utiltity other than in rare situations where calculation of free cortisol adds clinical value to the patient's management, almost always in specialist settings. This would typically be where a total cortisol result (usually on stimulation testing) seemed inconsistent with the patient's clinical presentation. CBG is therefore considered a specialist test (Tier 2).

Salivary cortisol measurement is appropriate for the evaluation of patients with possible Cushing's syndrome.[2] Since saliva reflects the level of free cortisol in the tissues (salivary glands), it provides an indirect measurement of tissue cortisol exposure. Normal, unstressed patients show a marked fall in salivary cortisol in the late evening, whereas in patients with Cushing's syndrome cortisol levels, and salivary cortisol, remain elevated.[7] However, as with 24 hour urine free cortisol tests, other non-Cushing's causes of elevation can occur, such as patients with significant physical or psychological stress. A late night (10 – 11 pm) saliva sample can be collected by patients before bed and sent to the laboratory the following day.

Measuring salivary cortisol samples or profiles at other times of the day as a means of assessing tissue cortisol exposure, and thereby diagnosing cortisol excess or deficiency (organic or functional, "adrenal fatigue") is considered unproven and lacks sufficiently robust evidence at this time to justify public funding.

Tests of thyroid function

No restrictions or guidelines around thyroid stimulating hormone (TSH), Free T4 (FT4)and thyroid antibody testing have been included in the recommendations (these are all Tier 1 tests), but formal schedule guidelines on tests of thyroid function are planned.

It is important to note that:

- **FT4** is not considered an appropriate initial request for the routine assessment of thyroid status unless an unusual cause, such as pituitary disease (secondary hypo- or hyperthyroidism) is suspected. When this is not specified, reflex addition of FT4 occurs in most laboratories when TSH is abnormal.
- **The FT4/FT3** ratio may be influenced by a range of factors including drug treatment, illness and fasting status. While it may also be influenced by some trace elements such as iodine and selenium it was not considered a sufficiently reliable marker for this purpose.
- **Thyroid peroxidase (anti-TPO)** is considered the appropriate first-line antibody test for autoimmune thyroid disease. Anti-thyroglobulin may add some value when anti-TPO is raised but can cause confusion when raised in isolation. Anti-thyroglobulin testing is important, however, in the management of patients

with thyroid cancer. Repeated monitoring of anti-TPO titre has been advocated in the monitoring of iodine status, but there is little substantive evidence base for its value in this context.

FT3

Free T3 (FT3), and its precursor FT4, levels are patient-specific with an individual "set point" much narrower than the population range. This is mostly due to individual variation in tissue sensitivity to thyroid hormone, but also other factors, such as the enzymatic conversion of T4 to T3 by tissue deiodinases (mainly type 1 in the liver). This is influenced by factors such as recent calorie intake, mineral status (such as iodine and selenium), growth hormone levels and thyroid status itself.

While all routine thyroid tests (TSH, FT4, FT3) can be affected temporarily by factors such as illness and drugs, FT3 is particularly affected by illness and also by reduction in calorie intake, with both of these causing a rapid decrease in plasma level.

FT3 requests are justified in the following circumstances:

- If TSH is low and FT4 is normal (to exclude T3 toxicosis): FT3 is routinely added by most laboratories in this situation, even if not requested
- When hyperthyroidism (including secondary hyperthyroidism) is suspected or monitored based on clinical details
- If there is known or suspected pituitary/hypothalamic disease: FT3 is not considered appropriate, however, for routine monitoring of primary hypothyroidism
- In patients with thyroid cancer, where FT3 measurement is occasionally helpful to monitor the degree of replacement (which in advanced cases can be above physiological requirements)

In early hyperthyroidism or primary hypothyroidism (thyroid failure, most often Hashimoto's disease) the serum level of TSH falls, or rises, early and is a sensitive biomarker of tissue exposure. It is therefore the single most useful initial test when either primary hyper- or hypothyroidism is suspected. Serum levels of FT4 and FT3 may rise and fall compared with the patient's individual set point, but typically initially remain within population limits.

In primary hyperthyroidism FT3 may rise above population limits before FT4 (so-called "T3-toxicosis"), and it is useful to perform a FT3 assay when TSH is low (typically suppressed to unmeasurable levels in true hyperthyroidism) but FT4 is within reference limits.

In secondary hyper- or hypothyroidism (pituitary/hypothalamic disease) TSH measurement alone is unreliable, and it is very important to measure FT4 in such patients, both for initial screening/evaluation and in monitoring. FT3 measurement can also be useful, especially if there is an abnormality of growth hormone production (growth hormone insufficiency can reduce the conversion of FT4 to FT3).[8]

While theoretically the plasma level of FT3 can be of value in assessing patients with hypothyroidism, there are many factors that confound interpretation, such as the individual patient set-point (which is unknown), recent illness or calorie and iodine intake. In patients with primary hypothyroidism and in iodine deficiency FT3 levels are generally preserved within population limits until relatively late (unlike in hyperthyroidism), making it an insensitive marker.

In patients taking T3 replacement, either alone or in combination with T4 (e.g. whole thyroid extract), FT3 levels rise and fall significantly depending on time of last dose and are not considered sufficiently reliable for monitoring. As with patients taking conventional replacement treatment, TSH is considered the primary analyte by which to adjust dose.

Tests of pituitary function

Insulin-like growth factor 1 (IGF-1) is an accepted test for the initial investigation of growth hormone excess (acromegaly, gigantism), and in monitoring the treatment of such patients. Since identification of acromegaly is important and the test has well-established clinical utility (even though the diagnosis is rare), writing "*possible or known acromegaly*" on the request form is sufficient for the test to be funded.

IGF-1 may also be requested, when recommended by a Chemical Pathologist or Endocrinologist, as an initial investigation of the possibility of growth hormone deficiency. However, interpretation is much more likely to be confounded by other factors, such as nutritional status, oestrogen and thyroid hormone status. A low result is more likely to be clinically significant when prior suspicion is high, e.g. patients with other anatomical or biochemical evidence for pituitary disease. Formal diagnosis of growth hormone deficiency (i.e. to qualify for publically funded treatment) requires further testing in a specialist setting.

Measurement of IGF-1 in patients on certain weight loss diets, e.g. the intermittent fasting ("5+2") diet, is not considered sufficient reason to justify public funding.

Growth hormone measurement can be helpful in the evaluation of patients with pituitary disease, particularly when acromegaly is suspected or in children or adults when there is suspicion of hypopituitarism. The test is funded if one of these indications is specified on the request form, or when ordered by an Endocrinologist.

A major problem limiting interpretation, however, is that growth hormone is secreted in a pulsatile fashion, so unless a result is clearly high or low, a single isolated result can be impossible to interpret. Stimulation or suppression tests, or serial measurements throughout the day, provide additional information; this should only be carried out under specialist management or recommendation.

Assessment of pancreatic disease and obesity

Plasma insulin levels are a key measurement when establishing a diagnosis of insulinoma as a cause of recurrent hypoglycaemia; since insulin has a plasma half-life of minutes and insulin secretion is shut off by hypoglycaemia in normal patients, plasma insulin levels should be suppressed. As evaluation of possible insulinoma is complex, prior discussion with an Endocrinologist or Chemical Pathologist is recommended before requesting this test.

When considering possible insulinoma it is critical to:

- Measure venous plasma glucose concurrently, so that the plasma insulin level can be properly interpreted. If the plasma glucose is > 3 mmol/L, then there is no stimulus to shut off pancreatic insulin release and plasma insulin level will be unhelpful
- Document any hypoglycaemic symptoms at the time, particularly those associated with poor glucose supply to the brain (neuroglycopaenic symptoms), such as confusion, "absence" and disorientation
- Document fasting status or time since last meal

Patients who have had bariatric surgery can develop excessive inappropriate pancreatic insulin secretion. For these patients, measuring insulin and glucose together at the time they describe symptoms is considered reasonable for any referrer, as long as the clinical information details that the patient had previous bariatric surgery.

While controversial, the biochemistry subgroup felt that evidence to justify funding of plasma insulin to identify insulin resistance and the metabolic syndrome was not sufficiently robust to justify public funding, except in specialist settings and then preferably when used as part of a calculation incorporating concurrent glucose level. For example, calculation of the HOMA index of insulin resistance may be useful in assessing the probability of non-alcoholic steatohepatitis (NASH) and the need for liver biopsy to assess fibrosis.[9, 10]

Insulin levels are not useful in patients with diabetes, as they can range from very high to unmeasurably low. They should also not be used to decide whether a patient has type 1 or type 2 diabetes; other tests such as diabetes-related antibodies (anti-GAD, anti-IA2) and plasma C-peptide have greater utility.

C-peptide is stored in secretory granules with insulin and co-released in equimolar amounts. Measuring plasma C-peptide is useful in the context of evaluating possible excess endogenous insulin secretion (e.g. insulinoma) and distinguishing this from exogenous insulin administration or another cause. Fasting status or relationship to meals should be well defined and plasma glucose should be measured concurrently. Ideally the sample should be taken during a spontaneous hypoglycaemic attack or a controlled fast, with careful correlation with symptoms. C-peptide is filtered by the glomeruli and caution should be exercised in patients with reduced GFR as this may lead to elevated values independent of any changes in pancreatic status. C-peptide may also be helpful in classifying some patients, when there is uncertainty as to whether they have type 1 or type 2 diabetes.[11] The utility of C-peptide for assessing insulin resistance is limited and it is not recommended for this purpose.

Nutritional markers: Essential fatty acids, vitamins, iodine and trace elements

Essential fatty acids (EFAs) are divided into two main classes: omega-3 and omega-6. The shortest chain omega-3 essential fatty acid is linolenic acid, and the shortest omega-6 is linoleic acid.

The most well known longer chain EFAs are:

- Omega-6 – arachidonic acid (C20:4n6), a precursor to prostaglandins and leukotrienes
- Omega-3 – eicosapenatenoic acid (C22:5n3 – EPA) and docosahexaenoic acid (C24:6n3 – DHA) ('fish oils')

There is considerable literature on the biology and benefits of n3 and n6 EFAs, and increased intake of omega-3 rich foods has been reported to have beneficial cardiovascular and anti-thrombotic effects, as well as a wide range of other less well substantiated benefits. There are also some isolated reports that higher plasma levels of some EFAs in plasma and/or red cells are associated with better long-term outcomes, but randomised trial evidence using plasma levels as a marker is currently limited.

EFA testing is technically difficult and very expensive. This test is not appropriate for patients who are considering or taking EFA supplements. Based on current evidence, knowing the detailed composition of EFAs in plasma and red cells was not considered sufficient to justify publically funding such requests at this time. Targets to guide treatment are not clearly established, correlation with tissue levels is imperfect, and there is potential for confusion due to the range of other biological and dietary influences. Achieving an appropriate balance of EFAs is important in some limited clinical settings, such as patients with severe liver disease or short bowel syndrome on intensive nutritional support. An EFA test would be appropriate in this setting.

Vitamins B1 (thiamine), B2 (riboflavin), and B6 (pyridoxine)
Plasma levels of these vitamins are sometimes requested as part of an overall nutritional or wellness screen. However, clinically significant deficiency is rare in New Zealand, except in the context of significant malnutrition or malabsorption, and/or liver disease (e.g. alcoholism). All of these vitamins are water soluble with very limited storage in tissues such as fat, hence plasma levels will be very influenced by recent short-term intake.

The assays are all expensive and there are significant pre-analytical factors of collection, processing and storage to consider which, if not addressed correctly, will invalidate the result. Even if the patient is suspected to have a deficiency, testing is often unhelpful as the turnaround is slow. The clinical response to vitamin supplementation is more helpful in confirming the diagnosis, and is the only way to prove that symptoms leading to the suspected diagnosis were related to deficiency of that particular vitamin.

Patients who have had bariatric surgery are predisposed to vitamin and trace element deficiency, in some cases leading to short and long-term neurological complications, including Wernicke's encephalopathy, polyneuropathy and visual defects. Post-operative monitoring of nutritional status is considered appropriate in this situation and requests for vitamin B1 and B6 are approved.[12] Measurement of vitamin B6 (pyridoxine) is justified in a specialist setting, when investigating a patient with raised homocysteine levels.

Vitamin D has a central role in bone and calcium metabolism and vitamin D tests were developed for investigation of abnormalities of calcium metabolism as well as metabolic bone disorders, such as rickets and osteomalacia. In recent years an association has been reported between low vitamin D levels and a very wide range of disorders (cancers, cardiovascular disease, diabetes, autoimmune disorders and infectious diseases). However, a causal link has yet to be demonstrated for any of these conditions.[13–15]

Despite this, the number of requests for vitamin D tests has increased dramatically, with many patients who get reasonable sun exposure and who are otherwise at relatively low risk, wishing to know their vitamin D level.

A comprehensive literature review for the Ontario Ministry of Health concluded that there is little evidence that it is useful to test vitamin D concentrations in patients without symptoms of metabolic bone disease.[16]

It is not necessary to routinely measure vitamin D in patients with low bone density. It is reasonable to routinely provide vitamin D supplements (1.25 mg or 50,000 IU cholecalciferol per month), without testing vitamin D, to frail housebound or institutionalised elderly people, or those in the community who avoid sunlight for cultural or medical reasons.

Requests for a vitamin D test should clearly indicate a high risk of vitamin D/calcium abnormalities for investigation, e.g:

- Rickets or osteomalacia, known osteoporosis, abnormalities of calcium/phosphate metabolism, raised ALP with likely bone cause
- Cystic fibrosis, special diets (e.g. PKU), renal transplant, anticonvulsant use
- Children (16 years and under) and refugees
- Prior to treatment with interferon for hepatitis C

 For further information see: "Vitamin D supplementation: navigating the debate". BPJ 36 (Jun, 2011).

Vitamin K is a fat-soluble vitamin important in the post-translational modification (gamma-carboxylation) of a

number of proteins, importantly some clotting factors (II, VII, IX and X), and also certain bone proteins. Measuring vitamin K levels directly is rarely helpful except in limited specialist settings.

People at risk of vitamin K deficiency include those with fat malabsorbtion (e.g. chronic pancreatitis, cystic fibrosis, parenteral nutrition) and some neonates. However, a vitamin K test is not indicated as part of the general investigation of nutritional status and possible malabsorption.

The appropriate investigation of patients with clotting disorders due to possible vitamin K deficiency is the direct assessment of clotting status (raised prothrombin time and, if more severe, raised activated partial thromboplastin time). Echis ratio (a further test of clotting) may also sometimes be helpful. Plasma levels of individual clotting factors can also be measured if required.

Coenzyme Q10 (CoQ10, vitamin Q, ubiquinone) is important in mitochondrial oxidative metabolism and energy production, as well has having natural antioxidant effects. The most clearly established reason for measurement is the investigation of rare inborn metabolic defects, in which there may be primary or secondary CoQ10 deficiency.

Plasma CoQ10 measurement has been suggested to be useful in statin-induced myopathy, heart failure and neurological disorders such as Parkinson's disease. There is biological rationale for an intracellular deficiency of CoQ10 as a factor in these conditions. However, the correlation between plasma and intracellular (e.g. muscle biopsy) levels of CoQ10 is limited. Since CoQ10 is also mostly carried in the lipid fraction, statin treatment will inherently lower CoQ10 levels independent of those in tissues. Therefore this test is not recommended for this purpose.

Some evidence suggests that low CoQ10 predicts worsened mortality in heart failure and achieving a higher level may be associated with a better outcome in patients taking supplements. However, other trials have suggested no benefit and the value of measuring CoQ10 in these conditions at this time awaits further evidence.[17, 18]

For these reasons the group recommended CoQ10 measurement should be restricted to Cardiologists, Neurologists and Paediatricians managing patients with the above disorders.

Although it has been advocated, the use of CoQ10 measurement and treatment in chronic fatigue syndrome has weak evidence-base.

Urine iodine levels reflect recent iodine intake and vary widely from day to day depending on recent food intake; even a patient with relatively low body stores can have normal excretion if analysed within two to three days of an iodine-rich meal (foods rich in iodine include most seafood and seaweed, eggs/poultry, milk and sometimes soy products). Routine urine iodine testing has no established role in general practice, and there is no evidence that it leads to any beneficial outcomes in patients who are appropriately monitored for hypothyroidism and appropriately supplemented in pregnancy. Routine inclusion of iodine in a vitamin supplement (but not iodine testing) has been recommended in women who are pregnant by the Royal Australasian College of Obstetricians and Gynaecologists.[19]

The median urine iodide level in a population can be used as an index of population iodine status, however, urine iodine excretion (both spot urine iodine creatinine ratio and 24h excretion) has very low predictive value for iodine deficiency in an individual patient. WHO guidelines for population medians do not apply to individual subjects and will grossly over-diagnose iodine deficiency if misapplied in this way.[20] At least ten urine iodine collections are needed to provide a reasonable estimate of iodine status.[21] The earliest functional evidence of iodine deficiency is a rise in TSH, which can be treated with iodine supplementation.[21]

Currently the only clearly established use of measuring urine iodine in individual patients is in the assessment of patients undergoing radioiodine treatment, where high urine iodine suggests poor thyroid radioiodine uptake and reduced treatment efficacy. It is also sometimes helpful in the evaluation of patients with hyperthyroidism.

Zinc, copper, and selenium, mercury, chromium and cobalt. Unless there is a high pre-test probability of deficiency (i.e. a pre-disposing condition, such as gastrointestinal disease), or toxicity (e.g. workplace exposure) it is rarely necessary to measure plasma copper, zinc, selenium or blood mercury in patients in general practice. Deficiencies of zinc or selenium do not occur in people who consume a reasonable diet and have normal gastrointestinal function.

Measurement of these trace elements may be useful in the management of patients predisposed to deficiency by malnutrition and/or gastrointestinal disorders and especially in patients taking parenteral nutrition.

Measurement of plasma and urine copper levels are also useful in the diagnosis and management of Wilson's Disease (clinical details should state "? Wilson's Disease" or "raised LFTs") and in rare genetic disorders of copper metabolism (e.g. Menke's syndrome).

These tests are also helpful in cases of zinc, copper and selenium poisoning, and cases of suspected poisoning are an indication for referral. Measurement of whole blood and urine mercury are of value in monitoring workplace exposure and when mercury poisoning is suspected.

Measurement of serum cobalt and chromium is indicated in patients with concern over possible overexposure. The most common situation is patients with a metal-on-metal joint prosthesis where there is concern over possible deterioration of the joint surfaces, and who may present with symptoms such as pain, swelling, limping or trouble walking, or noise coming from the joint. If cobalt and chromium levels are abnormally elevated, it is recommended to repeat the tests after three months. If levels from the second test remain abnormally elevated, discussion with the Orthopaedic Surgeon is recommended.

For further information see: "Testing serum cobalt and chromium in people with metal-on-metal hip replacements". Best Tests (Dec, 2012).

High levels of cobalt and chromium can also occur in people working with ceramics or metals, excessive supplement intake or renal impairment. Urine testing is more appropriate than serum for assessing chronic occupational exposure.

Evidence was not considered sufficiently robust to justify the public funding of measurement of plasma zinc or the zinc/copper ratio in patients with depression, autism, other mental health disorders or chronic fatigue syndrome. Results of these tests are often misleading because low plasma zinc and raised copper levels are non-specific changes commonly seen in inflammatory states and chronic disease.

The presence of amalgam dental fillings or symptoms of fatigue, depression, cognitive decline etc. are not sufficient indications for measurement of blood or urine mercury levels. The major determinant of blood mercury is dietary fish intake, and amalgam fillings do not cause a clinically significant increase in blood mercury levels.[22]

Tumour markers

These include:

- Acid phosphatase
- CEA
- CA125, C15-3, CA19-9, CA72-4

Apart from acid phosphatase (Page 12), no formal restrictions have been placed on these tests at this time (Tier 1), however, guideline recommendations for requesting them have been developed.

The guidelines recognise the value of these tests for monitoring known malignancies of specific types in specific clinical settings. They can also be useful for diagnosis in patients with a high probability of cancer at presentation, e.g. CA125 in patients presenting with a suspicious ovarian mass, and can provide prognostic information.

Virtually none of the typical tumour markers are completely specific for malignancy, or for a particular type of malignancy. For example, while often thought of as useful in ovarian cancer, CA125 can also sometimes be raised in other malignancies such as pancreas, lung, breast, endometrium and non-Hodgkins lymphoma. It can also be raised in a wide range of benign disorders such as acute and chronic liver diseases, acute and chronic pancreatitis, rheumatoid arthritis, ulcerative colitis, endometriosis, menstruation, non-malignant ascites and pleural effusions and SLE. Similarly, while a very high CEA is strongly suspicious for malignancy, it can be raised in a wide range of cancers (e.g. gastrointestinal, lung, thyroid, breast), and also in benign diseases such as hepatitis.

The role of most soluble tumour markers in screening is still under evaluation but they are not currently recommended for this purpose in the general population based on insufficient large trial evidence for benefit.

As an example of the recommendations, the indications for measurement of CA125 are:

- Patients with symptoms or signs associated with high suspicion of ovarian cancer: persistent continuous or worsening unexplained abdominal or urinary symptoms, pelvic mass
- Case detection in patients at high risk of familial ovarian cancer
- At diagnosis of ovarian cancer to provide prognostic information
- After treatment to monitor response and detect relapse

However, measurement of CA125 is not indicated for:

- Investigation of non-specific symptoms, when probability of malignancy is low
- Screening of asymptomatic low risk population (in a low risk patient a mildly raised result is much more likely to be a false positive rather than a true positive)
- Investigation of other suspected malignancies

Lipid and cardiovascular disease related tests

Apolipoproteins B (ApoB) and A1 (ApoA1). These tests measure the protein component of lipid particles, LDL (ApoB) and HDL (ApoA1) respectively. Since there is only one ApoB or ApoA1 molecule per particle, they give an estimate of particle concentration rather than total cholesterol concentration in those particles.

At present there are no restrictions on requesting these tests as the demand for them is very low, and there is little evidence that they are being inappropriately ordered.

A number of epidemiological studies (but not all) suggest that these tests, and their ratio, may be marginally more predictive than lipid measurements themselves. They may identify some patients with genetic dyslipidaemias, and possibly help identify residual risk in patients on aggressive statin treatment.

These tests are significantly more expensive than lipid tests and while there measurement is improving, they are less well standardised internationally. Their advantage of being able to be measured in the non-fasting state is of limited practical value as non-fasting lipid tests themselves are usually reliably interpreted in most patients.

For further information see: "Fasting may be unnecessary for lipid testing", Best Tests Nov, 2013.

Lipoprotein (a) is a weak independent risk factor for premature coronary artery disease and thrombosis in the general population. Lp(a) levels are mainly genetically determined, change little over time, and are poorly responsive to diet or to lipid-lowering treatment. There is very limited evidence to support whether Lp(a) reduction reduces the incidence of cardiovascular events.

Based on current evidence, the group considered that measuring Lp(a) is not indicated as part of routine cardiovascular risk assessment in primary care.[23] If the clinical approach is otherwise clear based on other risk factors, then measuring Lp(a) has little additional value. The group recommended that requests for Lp(a) be funded (once only per patient) when requested by Cardiologists, as part of a specialist lipid/metabolic clinic, or with prior Chemical Pathologist approval.

Measurement should be limited to certain uncommon situations, particularly:

- Patients in whom assessment using traditional Framingham risk markers may be unreliable, e.g. an unexpectedly early personal history of CVD, or significant family history in the absence of clear Framingham risk factors
- Where measurement may influence the decision of whether or not to start the patient on pharmacological treatment based on other risk factors

For further information, see: "Assessing cardiovascular risk: what the experts think". BPJ 33 (Dec, 2010).

Lipoprotein electrophoresis was historically used to classify patients with likely familial dyslipidaemias (Frederickson classification), with interpretation being based on the staining pattern and intensity of different lipid fractions. However, this classification is now rarely used, electrophoresis is expensive and there are other clinical and laboratory means of recognising primary lipid disorders (e.g. apolipoprotein measurements, genetic tests). The group considered that lipoprotein electrophoresis should only be funded in specific clinical circumstances when requested by Cardiologists, Endocrinologists/metabolic specialists or Internal Medicine specialists.

The major remaining application of electrophoresis is when considering the rare diagnosis of type III dysbetalipoproteinaemia (broad beta or remnant removal

disease). Such patients have palmar xanthomas and increased concentrations of apoB-containing remnant particles (VLDL remnants, IDL).

High sensitivity CRP. Inflammation is now considered to play an important role in atherosclerosis. In well, asymptomatic patients the baseline level of CRP (referred to as high sensitivity CRP or hs-CRP) is thought to reflect the underlying level of inflammation and to have a graded association with CVD risk. There is epidemiological evidence linking levels of CRP with levels of cardiovascular risk, however, recent data has suggested that the risk is not as strong as originally stated. Genetic studies also fail to support a clear causal link of hs-CRP with cardiovascular disease. The group recommended that hs-CRP is funded when requested or pre-authorised by a Cardiologist, specialist lipid, metabolic or cardiovascular disease clinic or a Chemical Pathologist.

It is thought that hs-CRP is able to refine CVD risk in people rated at intermediate risk with traditional risk factors, and thereby re-categorise them above or below a treatment threshold. However, no current guideline (including local guidelines) recommends using hs-CRP as part of routine risk assessment. The American Heart Association suggests that this use be at the physician's discretion, especially in the context of deciding whether or not to prescribe a statin.

Recent data has suggested that using the value for hs-CRP in the Reynolds modification of the Framingham equation does not sufficiently alter risk in most patients at intermediate risk to be cost-effective.[24] The current risk calculator used in New Zealand also does not allow data for hs-CRP to be used.

There is also debate about the validity of the main intervention trial (Jupiter trial) that has been quoted to support the use of stratification by hs-CRP to guide treatment with statins. Further analyses of this and other large randomised trials shows the relative benefit from statin treatment is similar regardless of initial CRP level, i.e. the test does not identify a unique group that is likely to benefit.[25, 26]

Homocysteine is a sulphur-containing amino acid interconverted with methionine in a very important cycle of intermediary metabolism (methylation cycle), in which folate and vitamin B12 are required co-factors. Deficiency of folate and vitamin B12 may be associated with raised homocysteine, but measurement of these vitamins directly is generally considered adequate to assess the patient's nutritional status.

Population evidence shows raised plasma homocysteine levels to be associated with long-term cardiovascular risk, however, intervention trials using B vitamin supplementation (folate, B12, B6) to lower homocysteine have been disappointing, suggesting such supplementation may be associated with worse outcomes.[27] It is therefore most likely that mild/borderline homocysteine elevation is not itself causative of vascular disease, but rather may be a marker of other more complex predisposing nutritional factors. Regardless, since modifying homocysteine has been proven to be of little benefit its measurement as a cardiovascular risk marker was not considered sufficient to justify public funding.

Measuring plasma homocysteine is indicated when a monogenic disorder of methionine and homocysteine metabolism is suspected, e.g. patients with early or atypical thrombosis (including presentations such as retinal vein thrombosis), and when homocystinuria is otherwise suspected on clinical grounds.

Homocysteine elevation has also been suggested to be a marker of long-term risk of neurodegenerative diseases, such as Alzheimer's disease. A recent systematic review suggested there may be a weak association between raised homocysteine and dementia risk, but the evidence was of very low quality.[28] As with vascular disease, there was no proof of causal relationship, and no proof that lowering homocysteine mitigates this risk. Raised homocysteine is also associated with other factors which are themselves known to increase long-term dementia risk, such as diabetes, renal impairment, and advancing age.

Outdated tests

The following tests have been replaced in favour of other tests with greater clinical utility in most situations.

Prostatic acid phosphatase. For the diagnosis and monitoring of prostate cancer this test has been almost entirely superceded by PSA, which has much higher sensitivity for early disease, better correlation with tumour burden and treatment response and is more sensitive in identifying residual disease. Acid phosphatase is also more affected by prostatic hyperplasia (BPH) and digital rectal exam (DRE) than PSA. International guidelines have therefore not recommended its use, as in the large majority of patients it has no proven clinical benefit in addition to PSA.[29, 30]

Prostatic acid phosphatase is raised in certain uncommon disorders such as Gaucher's disease, however, other markers are preferred. It has also been used historically as a marker of bone resorption, but has been replaced by other markers with better biological and analytical performance.

The group recommended measurement of acid phosphatase when referred or pre-authorised by an Urologist, Internal Medicine Specialist, Paediatrician or Haematologist (or when pre-approved by a Chemical Pathologist).

Creatine kinase MB (CKMB). This isoenzyme of CK is present in highest concentration in heart muscle, but is also widely present at lower concentrations in skeletal muscle. It was widely used historically in the diagnosis of myocardial infarction. However, troponin (T or I) testing is far more sensitive and specific and has a much wider diagnostic window, with detection of myocardial injury generally before CKMB is increased and for up to 10 – 14 days. Recent guidelines, both internationally and from the New Zealand Cardiac Society, recommend troponin as the marker of choice in the investigation of patients presenting with possible acute coronary syndrome.[31–33]

CKMB testing has been suggested to be useful in the evaluation of possible reinfarction, but with modern troponin assays a change in troponin is usually reliable. In some patients where there may be an analytical issue with a particular troponin assay, an alternative (either Troponin T or I, or a different manufacturer's assay) will usually solve the problem, avoiding the need for CKMB testing.

Faecal fat. Although used historically for identifying and monitoring patients with steatorrhoea, this is a poor screen as typically over 90% of pancreatic function must be lost before it becomes elevated. It is also a very unpleasant test for both the patient and laboratory. Most laboratories no longer offer faecal fat testing.

Measuring fat content in a small faeces sample can be performed by measuring a "steatocrit", or by visualising fat droplets using a fat stain (this detects the large majority of patients with moderate/severe fat absorption). Other tests such as faecal elastase are both more sensitive and less onerous for evaluating pancreatic enzyme insufficiency. The only remaining use of faecal fat estimates (as steatocrit) is in specialist settings, e.g. as a means of quantitating the degree of fat malabsorption in patients on close monitoring of replacement regimens.[34]

Fructosamine. For a wide range of reasons, both biological and analytical, fructosamine is an inferior test compared with HbA_{1c} for monitoring patients with diabetes. It has a much shorter window of monitoring glucose levels, has greater biological variation, and is affected by albumin turnover (especially significant proteinuria) and hydration status. International evidence for the long-term prognostic value of HbA_{1c} is far greater and treatment targets are much better established.

Fructosamine should only be measured when a reliable HbA_{1c} result cannot be obtained, e.g. in situations of altered haemoglobin turnover (e.g. ongoing active blood loss or venesection) and with certain uncommon haemoglobin variants. If a HbA_{1c} analytical interference is identified then other HbA_{1c} methods without interference can usually be found, which is the preferred approach (if in doubt the laboratory should be contacted to discuss).

In the rare situations where fructosamine testing is indicated, there is little value in measuring it more often than monthly.

Tests with insufficient evidence

These tests lack sufficient evidence to justify funding their analysis under any circumstances.

Red cell magnesium (RBC Mg). Plasma magnesium is considered to be adequate for assessment of magnesium status and there is insufficient evidence to justify the additional expense of RBC Mg measurement for any clinical purpose. Evidence linking red cell magnesium to chronic fatigue syndrome was felt to be unconvincing.[35, 36]

Salivary progesterone measurement has been advocated as a means of monitoring transdermal progesterone treatment in peri- and post-menopausal women. Serum progesterone levels in such women are very low, reflecting perhaps the poor systemic absorption of progesterone creams through the skin. The evidence base to justify public funding of the salivary progesterone test was considered insufficient by the group.[37]

Salivary testosterone levels add little clinical utility to a serum testosterone measurement. Levels in saliva are very low and in current assays the precision at these levels also hampers interpretation.

Underutilised, but expensive tests

The following tests have increasing evidence for their clinical utility when requested within appropriate clinical guidelines, but are relatively expensive.

In some cases tests were recognised as being very good tests in specific clinical circumstances and, even though expensive, were probably underutilised. However, there were also situations where their clinical utility was limited and when the temptation to request them should be avoided.

BNP and NTProBNP is an example of such a test.

It is recommended that BNP or NT-ProBNP is requested in the following situations:

- Exclusion of heart failure as a cause of unexplained breathlessness and other non-specific symptoms
- Management of anti-heart failure treatment (secondary role only, usually for difficult to treat patients). There were no formal restrictions recommended for non-cardiologists, but it is recommended that repeat testing occur no sooner than two weeks between tests and, additionally, no more than four tests per year, per patient (more frequent need than this suggests excessive use or need for specialist involvement)

These tests have high negative predictive value for the exclusion of undiagnosed heart failure in patients presenting with non-specific symptoms and not already taking anti-heart failure treatment. Conversely, a clearly high result supports the diagnosis of heart failure and also carries adverse prognosis, independent of other variables (although in most acute cases this is clinically obvious through other means). However, mild-moderate elevation does not exclude the possibility of some other cause of breathlessness besides, or in addition to, heart failure. These tests also do not completely avoid the need for echocardiography, which provides other important information on cardiac structure and function, such as cardiac valve anatomy and (regional) myocardial contractility and relaxation.

The value of BNP and NTProBNP is much less well established for guiding ongoing anti-heart failure treatment. While a rise or fall can sometimes help guide treatment, proof of outcome benefit is much more limited and at present these tests have a secondary role only. NHF/NZGG guidelines do not specifically restrict use in this setting but have not encouraged it and NICE guidelines (UK) recommend their use be restricted to challenging patients under specialist management.

It takes at least two weeks for a new equilibrium level to be established and repeat measurement within this time frame is not recommended. Patients with heart failure who are difficult to manage should be referred for specialist review.

The Laboratory Schedule Test List and Laboratory Test Guidelines are available from: **www.dhbsharedservices.health.nz**

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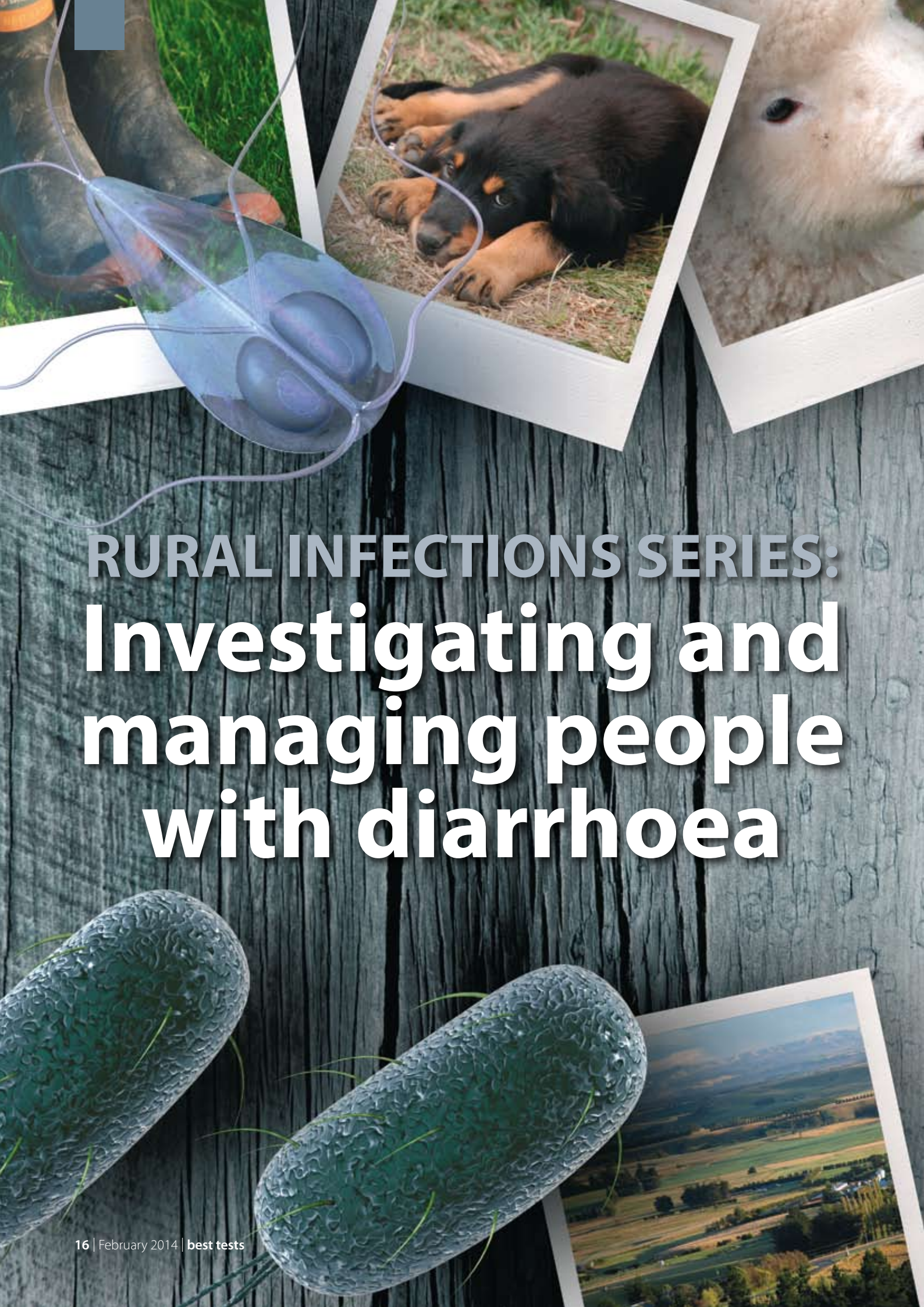

RURAL INFECTIONS SERIES:

Investigating and managing people with diarrhoea

Campylobacter, *Salmonella*, *Cryptosporidium* and *Giardia* cause diarrhoeal illnesses in thousands of people annually in New Zealand. The incidence of these infections is significantly higher in New Zealand compared to most other developed nations.[1] Animal, environmental and waterborne sources are a common cause of isolated illnesses and outbreaks, and exposure to these sources is a significant risk-factor for infection. This edition of the rural infections series focuses on these four notifiable pathogens, each of which causes a similar set of symptoms, and discusses the investigation and management of diarrhoeal illnesses in a person with rural occupation, residence or recent contact with animals or untreated water.

Infectious diarrhoea: the common quartet of causes

Campylobacter, *Salmonella*, *Cryptosporidium* and *Giardia* represent four of the five most frequently notified illnesses in New Zealand (pertussis is the fifth).[1,2] From July to September, 2013 (the most recent surveillance period*), these four pathogens caused a total of 50 outbreaks and approximately 2880 confirmed illnesses.[2] Rural occupation, living in a rural area or contact with farm animals is a significant risk factor for contracting these infections; approximately 10% of the notified cases in the reporting period were traced to an environmental, animal or waterborne source.[2] Any illness caused by these four organisms is notifiable to the Medical Officer of Health.

Campylobacter, *Salmonella*, *Cryptosporidium* and *Giardia* cause clinically similar illnesses, typically profuse diarrhoea, abdominal pain and nausea, with or without vomiting (Table 1, over page). Bloody diarrhoea, fever, malaise and a range of other symptoms may also be present. The patient's gastrointestinal symptoms usually last less than two weeks before resolving spontaneously, however, *Cryptosporidium* and *Giardia* can cause persistent or chronic diarrhoea in some people.

Viral infections and *E. coli* (VTEC, Page 18) are also common causes of diarrhoea in all patients.

* Data for *Giardia* comes from the previous quarter (April to June, 2013) as more recent data is not available

Diagnosis and assessment of infectious diarrhoea

Patients with *Campylobacter*, *Salmonella*, *Cryptosporidium* and *Giardia* infection will typically present to primary care with diarrhoea. History and examination is generally sufficient to establish a working diagnosis and appropriate management.

Diarrhoea can be defined by duration as follows:

- Acute – lasting less than 14 days (most infections from these four pathogens will be acute)
- Persistent – lasting between 14 – 30 days (*Giardia*, and occasionally *Cryptosporidium* can cause persistent diarrhoea)
- Chronic – lasting longer than 30 days

Finding the cause of diarrhoea

The patient's description of their symptoms and recent activity may suggest a cause for their diarrhoea. Enquire about:

- The characteristics of the diarrhoea, e.g. duration, consistency, the presence of blood
- Other general symptoms, particularly abdominal pain, fever, malaise or fatigue
- The patient's occupation (to identify people working in a rural occupation, food handlers and day care workers), where they live and any recent activity that may have increased the risk of environmental exposure, e.g. camping or tramping
- Any recent contact with farm animals or wildlife

- Recent contact with or ingestion of untreated water, e.g. effluent ponds, dams or tank water
- Where, what and when the patient ate prior to their symptoms starting, particularly asking about any high-risk food, e.g. chicken or seafood ingestion
- Other general risk factors, including recent international travel, similar symptoms in household members and recent hospitalisation or antibiotic use
- Risk-factors for non-infectious or non-gastrointestinal causes of diarrhoea, including family history of coeliac or Crohn's disease, symptoms associated with certain foods, e.g. following milk ingestion, if similar symptoms have occurred previously and the presence of any non-gastrointestinal symptoms

Defining the cause of diarrhoea

If the patient reports large-volume, watery or bloody diarrhoea with diffuse abdominal pain, enteric bacterial infection is likely.[10] In a person with a rural occupation, residence or recent contact with animals, *Salmonella*, *Campylobacter*, *Cryptosporidium* and *Giardia* are among the most likely causes, but other, more general causes of diarrhoea should also be considered, which would apply to patients in any setting.

If the patient' symptoms have occurred within six hours of ingestion of potentially contaminated food, food poisoning with pre-formed bacterial toxins (i.e. toxins that are present in the food and cause symptoms in the gut, rather than the bacteria themselves) should be suspected. However, the source of infection is not always apparent, or symptoms may occur coincidentally following ingestion of high-risk foods without being related.

Clinical differentiation between viral diarrhoea and an early presentation of enteric infection is difficult. Patients who have had diarrhoea for less than two to three days may have viral gastroenteritis, e.g. infection with norovirus, rotavirus or enteric adenovirus, or this may be an early presentation of enteric infection. The longer the patient's symptoms have been present, the more likely enteric infection becomes. In addition, viral gastroenteritis is less likely if the patient has bloody diarrhoea, fever and severe abdominal pain.[10]

Verotoxin-producing *E. coli* (VTEC)

Escherichia coli are common bacteria in the human gastrointestinal flora, and are not usually pathogenic. However, overgrowth and certain strains of *E. coli* can cause severe diarrhoea. The incidence of illness related to *E. coli* in New Zealand is significantly lower than that caused by *Campylobacter*, *Salmonella*, *Cryptosporidium* or *Giardia*. Infections often have an environmental or animal source; from July to September, 2013, there were five environmental, animal or waterborne outbreaks.[2] Food-borne illness also occurs, particularly following ingestion of contaminated meat.

E. coli itself is a causative pathogen in cases of notified gastroenteritis. Gastroenteritis is a notifiable illness if there is believed to be a common source or if the person with the illness is in a high-risk category, such as a food handler. In such a case, *E. coli* will be added retrospectively as the causative organism, if identified through laboratory testing.

E. coli must also be notified if a shiga-toxin producing (also known as verotoxin-producing *E. coli* or "VTEC") strain is found to be present. Only some *E. coli* can produce these toxins and cause disease if ingested.[8] The genes required to produce these toxins are thought to have been acquired from another, more pathogenic bacteria, *Shigella dysenteriae*, via bacteriophage transfer. The shiga toxin will only cause illness in certain species. Cattle, pigs and deer can carry shiga-toxin producing bacteria without developing an illness, but when spread to humans, the toxin produces symptoms ranging from mild diarrhoea to haemorrhagic colitis.[8, 9] Most infections are caused by ingestion of food or drinking water contaminated with faeces from ruminant animals.[9]

Table 1: The natural history and presentation of the four most common notifiable infections in New Zealand[3–7]

	Salmonella enterocolitis	Campylobacter enterocolitis	Cryptosporidiosis	Giardiasis
Organism	Bacteria	Bacteria	Parasite	Parasite
Mode of transmission	Primarily food-borne, but also stagnant water, animals (particularly birds), and person-to-person	Water, animals, food and person-to-person	Animals (particularly calves and lambs), water, food and person-to-person	Water, animals and person-to-person
Seasonality	Year-round	Spring and summer	Spring	Year-round
Incidence – Cases in previous 12 months*	1118	6212	1350	1654
Incidence –five-year trend**	Variable/Stable	Decreasing	Increasing	Decreasing
Diarrhoea duration	Usually less than 14 days	Usually less than 14 days	Usually less than 14 days, potential for persistence	Variable, from less than 14 days to more than 30 days
Diarrhoea symptoms	Profuse, watery and occasionally bloody	Variable severity, watery and often bloody	Profuse and watery	Greasy, malodorous, floating stool, i.e. symptoms of malabsorption
Incubation period, average (Range)	12 – 36 hours (6 – 72 hours)	2 – 5 days (1 – 10 days)	7 days (1 – 12 days)	7 – 10 days (3 – 25 days)
Nausea and vomiting	Nausea, occasional vomiting	Nausea and vomiting	Nausea and vomiting	Nausea, rarely vomiting
Fever	Common	Common	Common	Less common
Period of infectivity to others	Typically several days to several weeks after onset of symptoms, can be up to one year in children	Several weeks after onset of symptoms	Several weeks after symptoms resolve	Up to several months after onset of symptoms

* Incidence data are from July, 2012, to June, 2013.

** Change in incidence from December, 2009, to December, 2013.

Non-infectious causes of diarrhoea should also be considered. Patients with small-volume, bloody diarrhoea, lower abdominal cramping and tenesmus (feeling as though they constantly need to defaecate or that the bowel is not completely empty following a bowel movement), may have inflammation of the bowel due to a conditions such as coeliac disease or inflammatory bowel disease. Family history and the duration of symptoms may suggest non-infective causes; however, first presentations of these illnesses can be difficult to differentiate from an acute episode of infectious diarrhoea.

Non-gastrointestinal infections can sometimes cause acute diarrhoea and should be considered when symptoms suggest another system could be involved, including urinary tract infection, pneumonia, otitis media or systemic infections. In one United States study, retrospective analysis of patients initially diagnosed with gastroenteritis found that 8% had a non-gastrointestinal systemic infection.[11] Vomiting will usually be more prominent than diarrhoea in people with these infections.[12]

Assessing for dehydration

The examination should focus on identifying dehydration. This includes basic observations, with attention to skin turgor, mucus membranes and capillary refill rate, and an abdominal examination. Although rare, other possible complications of enteric infection causing diarrhoea include reactive arthritis and Guillain-Barré syndrome.[10]

Laboratory investigation

Laboratory investigation is not routinely required for patients with acute diarrhoea.

However, in a patient with a rural occupation, residence or recent exposure to animals, laboratory investigation is recommended to provide additional information to guide treatment and for notification purposes.

What tests should be requested for a patient with rural risk-factors?

In people with diarrhoea who live or work in a rural setting or with recent exposure to animals or untreated water sources, request: [13]

- Faecal culture and microscopy
- Faecal *Giardia* and *Cryptosporidium* antigen tests

Note the patient's relevant risk factors, e.g. rural occupation, on the laboratory request form, as the test may be declined by the laboratory if justification for testing is not recorded.

Only one stool sample should be sent for analysis. However, faeces are not homogenous; bacteria may not be evenly distributed within the sample and the volume of excreted bacterial material varies with the stage of infection. As a result, false-negatives can occur, particularly with faecal culture. A repeat test may be justified if a particular pathogen is strongly suspected and the initial test is negative and the patient has ongoing symptoms.[14] In this situation, discussing the patient with an Infectious Diseases Physician or Clinical Microbiologist should be considered.[14]

Faecal culture and microscopy

The faecal culture and microscopy test is used to assess a patient's stool for leucocytes, indicating inflammation of the bowel either due to an invasive pathogen or other inflammatory bowel disease and isolation of pathogenic bacteria. This is the first-line test for the investigation of infectious diarrhoea in someone with risk factors. It can identify *Campylobacter*, *Salmonella*, *Yersinia*, *E. coli* (VTEC) and *Shigella*.

Ask the patient to provide a faecal sample in a sterile collection container. The sample should be stored at room temperature and should not have a fixative applied to it. The sample should be transferred to the laboratory as soon as possible. If transfer will be delayed by more than 24 hours, refrigerate the sample and consult the collecting laboratory.

Giardia and Cryptosporidium testing

The *Giardia* and *Cryptosporidium* antigen test is an immunoassay test that identifies the presence of antigens from *Giardia* and *Cryptosporidium* in a patient's stool. The results will be reported as either positive or negative, i.e. antigens are present or absent.

As with faecal culture, an antigen test requires a fresh faecal sample. The same sample used for bacterial culture is used for the antigen test.

The antigen test has high sensitivity and specificity.[15]

Other tests are available, but less commonly used

Microscopy can be used to detect *Giardia* and *Cryptosporidium*, in samples from patients with acute diarrhoea, however, it is not routinely recommended. Microscopy is an alternative,

second-line option in a patient with a negative antigen sample but ongoing symptoms. Microscopy requires a high degree of technician skill, has a slower turnaround time and requires up to three serial samples in order to provide sufficient sensitivity, which decreases patient compliance and increases the cost of the test.

Other methods of detecting *Giardia* and *Cryptosporidium* such as microbial stains and enzyme immunoassays are available in some laboratories, but they are not routinely recommended. Stains require a different sample, with a fixative applied to the stool; this type of test would generally only be requested in consultation with an Infectious Diseases Specialist.

It has been suggested that real-time polymerase chain reaction (PCR) will eventually become the standard test for investigating infectious diarrhoea, due to a faster turn-around time, and may replace antigen testing.[16] At present PCR is not routinely available for investigating infectious diarrhoea.

Management of infectious diarrhoea

While awaiting laboratory results, management of the patient is similar to a standard case of gastroenteritis unless there is a strong clinical suspicion of a particular organism, e.g. confirmed household contacts. The focus of management is preventing or treating dehydration, and reassuring the patient that diarrhoeal illnesses are usually self-limiting.[17]

When should a patient be referred to hospital?

Most patients with infectious diarrhoea can be managed at home. However, referral to hospital should be considered for patients with persistent vomiting who are unable to retain oral fluids or who have severe dehydration. Referral should be considered for older patients who are unable to manage at home by themselves or younger children whose condition may deteriorate rapidly.[12] Some practices, particularly rural practices, may be equipped to manage patients with dehydration with IV fluids and monitoring, rather than referring to hospital.

For further information, see: "Community-based IV administration: primary care reducing hospital admissions", BPJ 38 (Sep, 2011).

The Laboratory Test Schedule

In October, 2013, the Laboratory Test Schedule and accompanying referral guidelines were released. DHBs can implement the guideline individually. All available laboratory tests have been categorised into two groups, termed Tier One and Tier Two. Tier One tests can be ordered by any clinician, Tier Two tests are limited to a list of named specialists. Guidelines for the appropriate ordering of selected tests were also developed.

Both faecal culture and *Giardia* and *Cryptosporidium* antigen test are funded Tier One tests in the Laboratory Schedule.

For further information, see: "The New Zealand laboratory test schedule and guidelines: What does it mean for general practice?", Best Tests (Nov, 2013).

Monitoring and preventing infectious disease in New Zealand

Notification and surveillance are key components of managing and preventing communicable illnesses in New Zealand. The data gathered from these activities guides the direction and scope of local and national public health efforts and campaigns.

The list of notifiable diseases was set out in the Health Act 1956, and is available from the Ministry of Health website. Illnesses are added to the list if they are deemed important to public health, e.g. avian influenza (H7N9) and Middle East Respiratory Syndrome (MERS) were added to the list in 2013.

All notifiable illnesses must be reported to the Medical Officer of Health once there is a reasonable clinical suspicion of the illness or confirmation through testing. Some illnesses, termed "Section A illnesses", must also be reported to the local health authority, e.g. the PHO or DHB.

Campylobacter, *Giardia*, *Salmonella* and *Cryptosporidium* are all Section A infectious illnesses. Laboratory testing is required to confirm the illness for notification. Both culture or antigen testing are sufficiently accurate for notification purposes.

In addition to the standard clinical tests performed for diagnosis, additional testing may be performed by the laboratory to provide better surveillance data for some notifiable illnesses. For example, *Campylobacter* bacteria identified via culture may undergo multilocus sequence typing in order to provide epidemiological data.[1] This information is not routinely provided to practitioners.

For further information, see: **www.health.govt.nz/our-work/diseases-and-conditions/notifiable-diseases**

Rehydration and preventing further fluid loss

Infants and children without signs of clinical dehydration, should continue breast feeding and other milk feeds as normal. Older children should be encouraged to drink regularly, in small amounts.[18] Oral rehydration solution can be offered as a supplemental fluid.[18] Oral rehydration solutions can be made at home (see recipe below) or prescribed, fully-subsidised. Drinking undiluted fruit juices or carbonated drinks should be discouraged,[18] as they contain high levels of sugar, and can increase dehydration through diuretic action and by altering the osmolality of the gut.

In infants and young children who are dehydrated, oral rehydration solution is recommended.[18] Chilling the oral rehydration solution (or freezing into ice blocks) can improve palatability. Fluids should be offered in regular, small amounts to help avoid vomiting. Replacement with 50 mL/kg over four hours is recommended.[18]

In adults with a diarrhoeal illness, oral rehydration solutions are not usually required. However, patients should be advised to increase oral fluid-intake to two litres per day, with fluids such as water or salty soups. As with children, adults should avoid sugary or caffeinated drinks, e.g. sports drinks. Advise patients to eat normally when they feel they are able; bland foods may be more palatable initially.

A recipe for oral rehydration fluid is:

- 1 litre of water
- 8 teaspoons of sugar
- 1 teaspoon of salt

Stir until dissolved and store in the refrigerator. The solution should be discarded after 24 hours.

For further information on the management of dehydration in people with gastroenteritis, see: "Assessment and management of infectious gastroenteritis", BPJ 25 (Dec, 2009).

Pharmacological management

Antibiotics are not recommended for people with acute diarrhoea of unknown pathology.[12]

Antibiotic treatment may be indicated for adults or children if a specific pathogen is identified by laboratory investigation

(Table 2, over page). Antibiotics are required for patients with giardiasis and symptomatic contacts of the patient. Antibiotic treatment may be appropriate in some patients with salmonella enterocolitis and campylobacter enterocolitis, depending on their risk-factors. *Cryptosporidium* is not treated with antibiotics, as they are not effective.

Antidiarrhoeal medicines are not routinely recommended and should not be used if the patient has blood or mucus in their stool.[12] In people with diarrhoea containing blood or mucus antidiarrhoeal medicines increase the risk of toxic megacolon and prolong duration of diarrhoea.[19] If an antidiarrhoeal is required for symptomatic relief in a patient without blood or mucus in their diarrhoea, loperamide can be considered.[12] Loperamide should be given at 4 mg initially, with 2 mg after each loose stool, up to a maximum of 16 mg in 24 hours.

Antiemetics are not routinely recommended.[12]

If pain relief is required, paracetamol can be given. NSAIDs should be avoided in people with dehydration or the potential for dehydration due to the risk of kidney injury.

The patient's current medicine use should also be reviewed, as certain medicines may worsen diarrhoea (e.g. laxatives), increase the risk of complications from the diarrhoea (e.g. diuretics, NSAIDs) or can be affected by diarrhoeal symptoms (e.g. reduced absorption of oral contraceptives).

Lactose intolerance or irritable bowel syndrome following infection

Secondary, or acquired, lactose intolerance can occur following any gastrointestinal illness that affects the gut mucosa. It is particularly common in adults following *Cryptosporidium* or *Giardia* infection and in children following any enteric infection.

Symptoms of lactose intolerance, shortly after consuming lactose, include:

- Diarrhoea
- Abdominal pain and distension
- Flatulence
- Dyspepsia

If the patient's diarrhoea continues following antibiotic treatment or begins again soon after symptoms cease consider lactose intolerance. A lactose challenge can be undertaken: instruct the patient to trial a lactose-free diet for two weeks, then reintroduce these foods, and report any symptoms that occur. All food containing lactose needs to be removed during the challenge, so food labels should be closely assessed. Many foods and some medicines contain unexpected lactose, such as instant soups, muesli bars and some processed meat.

Secondary lactose intolerance following enteric infection is usually transitory, but may persist for several weeks.[21] It can be managed with dietary restriction followed by gradual reintroduction of milk.

Irritable bowel syndrome may also develop following a significant enteric infection. Symptoms and signs will be similar to lactose intolerance; however, a lactose challenge will usually be negative. Irritable bowel syndrome may be short-term or may persist for several years. Management usually involves reassurance, stress management, lifestyle and diet changes and, in some patients, medicines such as loperamide and mebeverine.

For further information on lactose intolerance, see: "Investigating the gut: Lactose intolerance", Best Tests (Mar, 2010).

For further information on irritable bowel syndrome, see: "Irritable bowel syndrome in adults: not just a gut feeling", BPJ 58 (Jan, 2014).

Management of contacts

Symptomatic contacts should be managed based on their risk-factors and the severity of their illness.[3–6] For example, if they are a food handler or have a rural occupation, investigation may be required. If no risk-factors are present, investigation is not routinely recommended. A "probable" notification can be made based on contact with a confirmed case, without laboratory, testing if necessary.

Asymptomatic household contacts of people with salmonella enterocolitis, who are food handlers, should have a faecal culture and microscopy test requested to confirm they are not infected and can safely attend work (See Table 1 for incubation times).[4] Investigation, restriction from school or work and empiric treatment are not required for other asymptomatic contacts of people with notifiable infectious diarrhoea, although they should be made aware that if they develop symptoms, they need to present to primary care and will require assessment and potentially testing.[3–6]

Table 2: The management of four common causes of infectious diarrhoea [3,12,20]

Infection	When to treat with antibiotics	First-line	Comment
Salmonella enterocolitis	Treat patients with severe disease,* who are immunocompromised or who have cardiac valve disease or endovascular abnormalities, including prosthetic vascular grafts	Ciprofloxacin, 500 mg, twice daily, for three days Co-trimoxazole, 160 + 800 mg, twice daily, for three days is an alternative	Treatment may prolong excretion For children, discuss appropriate treatment with an Infectious Diseases specialist
Campylobacter enterocolitis	Treat if severe,* symptoms present for more than one week, women who are pregnant nearing term or people who are immunocompromised. Treatment may also be appropriate for food handlers, child care workers or people caring for immunocompromised people.	Erythromycin ethyl succinate 400 mg (child 10 mg/kg), four times daily, for five days** A second-line alternative for adults is ciprofloxacin, 500 mg, twice daily, for five days	Treatment has limited effect on symptoms, but may reduce stool carriage
Cryptosporidiosis	Antibiotics are not effective		Discussion with an Infectious Disease specialist is recommended for patients who are immunocompromised or have co-morbidities
Giardiasis	Antibiotic treatment is recommended if laboratory tests show infection is present (and for symptomatic contacts)	Children < 35 kg – ornidazole 125 mg/3 kg, once daily, for one to two days Adults and children > 35 kg – ornidazole 1.5 g, once daily, for one to two days Metronidazole can also be used first-line. Children – 30 mg/kg, once daily, for three days, to a maximum of 2 g per day. Adults – 2 g, once daily, for three days	If treatment with ornidazole appears to be ineffective, exclude re-infection from asymptomatic contacts; lower doses of metronidazole may be given for longer periods, e.g. 10 mg/kg/dose, three times daily for children or 400 mg, three times days, for seven days. An interval of two to three days between treatments is recommended. Ornidazole is only available in tablet form, which may be crushed. A child dose is equivalent to one-quarter of a tablet per 3 kg.

* High fever, bloody diarrhoea or more than eight stools per day[12]

** Erythromycin 800 mg, twice daily, can be considered for patients where adherence is likely to be an issue

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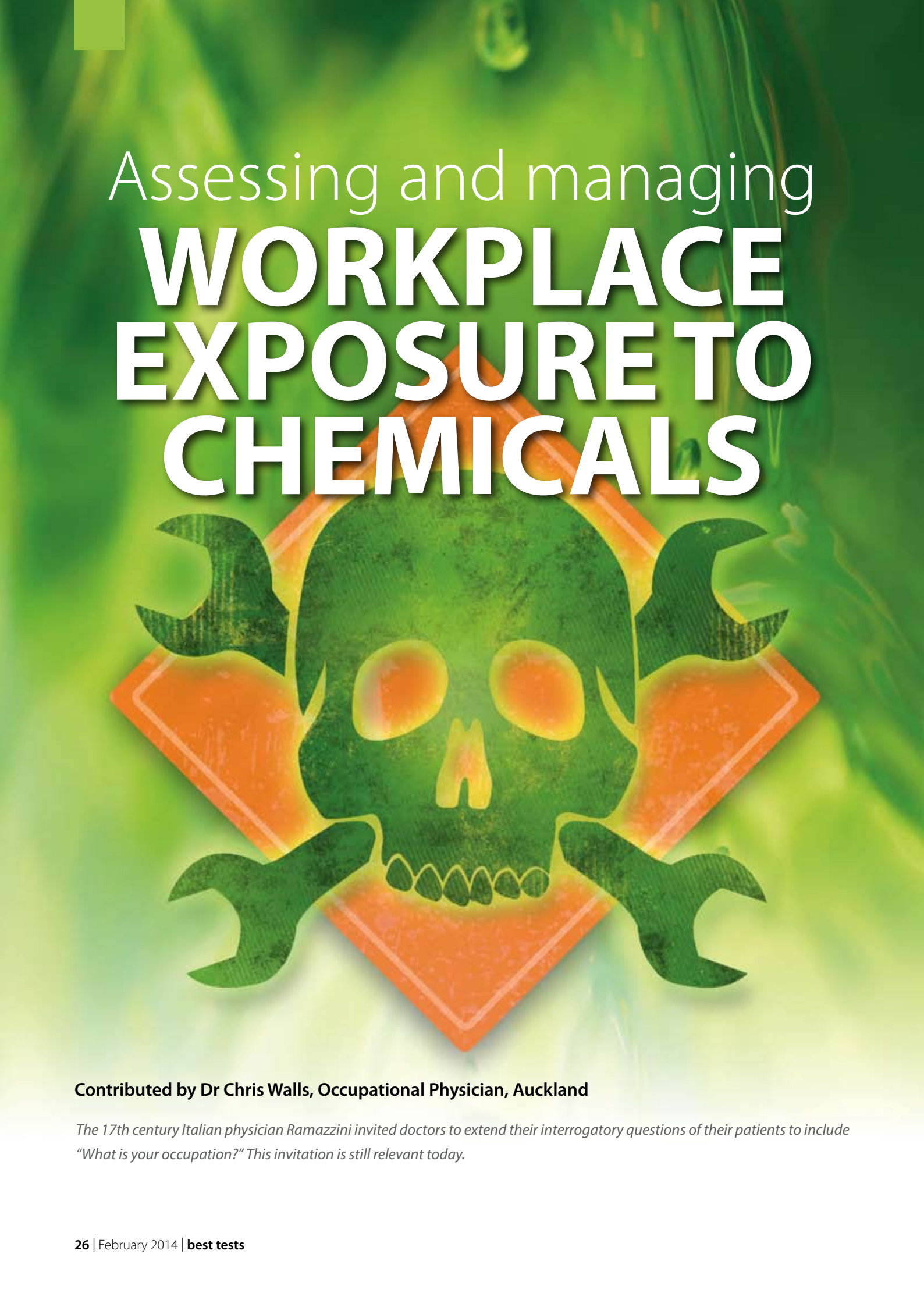
Assessing and managing WORKPLACE EXPOSURE TO CHEMICALS



Contributed by Dr Chris Walls, Occupational Physician, Auckland

The 17th century Italian physician Ramazzini invited doctors to extend their interrogatory questions of their patients to include "What is your occupation?" This invitation is still relevant today.

Many people present to their General Practitioner concerned about the possible health consequences of chemical exposures. Despite this, the health effects of the commonest workplace chemical exposures are often overlooked.

Assessment of patients with such exposures, and their clinical outcomes, is complex and difficult, with many cases presenting as more conventional illnesses. Failure to recognise a problematic exposure, coupled with on-going exposure, can lead to medical conditions that are difficult to manage.

Effective evaluation of possible chemical exposures contributing to a health concern requires consideration of a person's occupation as part of their clinical history, as well as some knowledge about the effects of specific chemical exposures.

The potential medical consequences of workplace chemical exposures

Workplace chemical exposures can result in the development of a new medical condition, however, the more common consequence is a worsening of a pre-existing condition. For example, a welder who has asthma may develop more brittle asthma as a result of exposure to welding fume.

The impact of adverse workplace exposures on a person with compromised health is often under-recognised. In such situations, the workplace exposure initiates the "illness cascade". For example, a worker who is obese, with poorly controlled diabetes, who smokes, and who works in an enclosed environment with petrol/ diesel powered equipment without adequate ventilation (carbon monoxide exposure), is suddenly required to undertake some excess physical activity (emergency response); this can lead to angina or collapse.

Assessing a patient's concerns

In order to detect health consequences from any exposure of concern, it is necessary to identify which substances are involved, and understand the likely effects of these chemicals. Patients who present with concerns about hazardous substance exposure without any particular exposure history (or specific substance of concern) are particularly challenging to assess.

Once the substance of concern has been identified, a clinical history should identify the patient's occupation and in particular what the tasks and likely exposures are. The health

Notification of disease and injury from hazardous substances exposure

Cases of injury or disease relating to hazardous substances, and wider poisonings arising from chemical contamination of the environment, require notification to the Medical Officer of Health under the Hazardous Substances and New Organisms Act 1996 and the Health Act 1956.

A short electronic notification form is available on the *bestpractice* dashboard (log in at www.bestpractice.org.nz or go directly through MedTech) – look for "Hazardous Substances & Lead Notifications". Primary care practices that do not use *bestpractice*, should still inform their Public Health Unit of any notifications. Access to the notification form for non-MedTech Patient Management Systems will be available later in 2014.

The employer is expected to notify the Ministry of Business Innovation and Employment when an illness arises from workplace exposures, but this is not a requirement of the General Practitioner.

ACC carries out its own determinations according to its Act, and it is possible for a worker to suffer a work related illness but not meet ACC's criteria for assistance.

Common illness presentations resulting from chemical exposures

Common workplace illnesses that are often misdiagnosed include:

- Metal fume fever or chemical pneumonitis ("welder's flu")
  - Sudden onset of fever, shortness of breath, cough and wheeze within 24 hours of exposure to metal or plastic fume from the welding process
  - Rarely diagnosed on the history; lung function tests are useful to confirm the diagnosis and recovery. A chest x-ray excludes other issues.
- Carbon monoxide exposure
  - Common, and occurs in unusual circumstances, e.g. prolonged chainsaw use in dense undergrowth
  - Often overlooked in the illness cascade leading to collapse
- Organic solvent exposures
  - Acute (intoxication) and chronic (encephalopathy) illness patterns from printing, painting/finishing and plastic industries
- Occupational asthma
  - From many industries, including pine wood processors, MDF manufacturing, cedar wood processing and car painting
- Pesticide/biocide exposures
  - Patients may present with chronic malaise, the cause of which can be difficult to confirm
  - Many of the more toxic biocides are no longer in use

consequences of chemical exposures depend not only on the material that people are exposed to but the route of exposure, metabolism and excretion. An important concept is "dose" – how much for how long?

The timing of symptoms is important. Symptoms that persist during an absence from work tend not to be related to the workplace. Ask about chronic effects of the exposure, but also try to identify episodes of acute toxicity around the exposure time. For example, pesticide spray exposures are often blamed for low grade chronic "unwellness" but a history of symptoms, such as acute malaise, skin rashes or shortness of breath, around peak exposure times (e.g. mixing concentrate, unexpected soakings) would suggest a more significant exposure.

Identifying health consequences of chemical exposure is only occasionally aided by specific testing of the patient or the workplace. These measurements are either of:

1. Exposure assessment, e.g. static sampling in a workplace or personal sampling of the worker (e.g. dust/fume measurements in the breathing zone of a welder). There are specific "acceptable" concentration limits for known hazardous chemicals (in New Zealand called Workplace Exposure Standards). However, measurement against these Standards is usually only done by concerned companies.
2. Effect assessment, e.g. peak flow measurements at work or away from work
3. Specific biological monitoring (very occasionally), e.g. blood lead levels

If physiological or laboratory measurements are possible, they might be taken both during and away from exposures.

In reality, there are few exposure assessment services available to General Practitioners, and physiological measurements ("effect assessments") are usually the only accessible tests in primary care.

There are currently few New Zealand governmental resources to assist General Practitioners with advice on assessment of workplace exposure to chemicals and illness this may cause. Potential sources of information/contacts include:

- The University of Otago Department of Preventive and Social Medicine

- The National Poisons Centre
- Occupational medical specialists
- Local occupational health services
- Medical literature

Other considerations

Many people at work fear that they place their job security at risk if they report their concerns about workplace conditions.

General Practitioners may be involved in a patient's dispute with their employer or the workplace insurer, e.g. providing a medical certificate. Such circumstances often complicate determining whether a workplace chemical exposure may be affecting their patient's health, confirming the suspected relationship, and advising on appropriate treatment or protection.

Management of occupational exposure

General Practitioners have two main roles in management of workplace exposure related illness: treating the symptoms, and providing the patient with appropriate information about preventing further exposures. An overall goal is to help the patient to maintain their work.

Many conditions are either self-limiting (the symptoms resolve when exposure ceases or shortly after) or can be attributed to historical exposures. Controlling the exposure at the source (e.g. ventilation, substitution with less toxic products) is optimal because it controls the symptoms and benefits employer and employee. In general, recommending "safety gear" (Personal Protective Equipment) is not a useful way to provide protection.

Where workplace chemical exposures cannot be reduced, or the health consequences of these are significant, advice about seeking suitable alternative work may be necessary. For example, when people develop allergies to workplace chemical exposures, they usually have to abandon that work.

The important message is that control of symptoms caused or worsened by workplace exposures becomes very difficult where the linkage between those symptoms and that exposure remains undetected. Enquire about a patient's occupation, and consider if workplace exposure to chemicals is causing or contributing to their symptoms.

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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