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Taking responsibility for test results

Haematology tests

Myalgia in patients taking statins

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better medicine

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Taking responsibility for test results:
A discussion

The management of test results, in particular the issue of who is ultimately responsible for following up these results, is at times contentious. There is often a lack of agreement and consistency between clinicians, practices and health organisations as to what is reasonable and practical. This is further complicated when multiple clinicians are involved in the management of a patient, especially when this spans both primary and secondary care. There are numerous pitfalls that can occur when managing patient test results and no management system is likely to be fail-safe. Responsibility for developing an effective method of managing test results lies with both the individual clinician and with the professional community within which they practice, e.g. group practice, hospital department, PHO, DHB. The following commentary is intended to provoke thought and discussion about the challenges faced by clinicians and health organisations in managing test results.

Cole's clinical investigation guidelines can be used as a framework

The Medical Council of New Zealand (MCNZ) endorses the use of "Cole's Medical Practice in New Zealand" for best practice principles for the appropriate follow up of patient test results.[1] Other relevant guidance includes "Managing Patient Tests Results – Minimising Error" produced by the Royal New Zealand College of General Practitioners (RNZCGP) and the RNZCGP's Cornerstone accreditation documents.[2, 3] The Health and Disability Commissioner also has an interest in the management of test results. Rulings on specific cases where test results have not been appropriately managed can be found on the HDC website: **www.hdc.org.nz/publications/other-publications-from-hdc/articles/2008/managing-patient-test-results**

Although there are some differences in the guidance offered, the overriding principles are the same: have a system to track and manage tests and define who is responsible for conveying information to the patient in a timely, clinically appropriate and meaningful manner.

The principles of Cole's

The Cole's Medical Practice in New Zealand guidelines (2013) are a set of principles intended for all registered doctors working in New Zealand. The guidelines are based on generally accepted standards of practice, and from case experience of disciplinary tribunals, in accordance with advice from the Health and Disability Commission.

Cole's lists eight key principles for managing clinical investigations, to ensure patient health and safety:[1]

1. If you request a clinical investigation, you should tell your patient why the clinical investigation is recommended and when and how they will learn the results
2. All the relevant parties should understand their responsibilities clearly
3. If you are responsible for conducting a clinical investigation you are also responsible for ensuring that the results are appropriately communicated to those in charge of conducting follow up, and for keeping the patient informed
4. If you are responsible for informing the patient, you should:
   - Inform the patient of the system for learning test and procedure results, and arranging follow up
   - Ensure that staff and colleagues are aware of this system
   - Inform patients if your standard practice is not to notify normal results and obtain their consent to not notifying
   - If other arrangements have not been made, inform the patient when results are received. This is especially important if the results raise a clinical concern and need follow up.

Cornerstone: effective systems for managing test results

Practices who wish to gain RNZCGP Cornerstone Accreditation must meet the following criteria in regards to managing clinical investigations:[2]

- There is a documented policy that describes how laboratory results, imaging reports, investigations and clinical correspondence are tracked and managed
- All incoming test results or other investigations are sighted and actioned by the team member who requested them or by a designated deputy
- Patients are provided with information about the practice procedure for notification of test results
- The practice can demonstrate how they identify and track potentially significant investigations and urgent referrals
- A record is kept of communication with patients informing them about test results

An overall aim is to ensure that the right people get the right information within the right time frame.

5. Identifying and following up overdue results is an essential, but [sometimes] difficult, office management task. Your system should ensure that test results are tracked successfully. Such a system might be a paper file or computer database that identifies:
    - High risk patients
    - Critical clinical investigations ordered
    - Dates of reports expected
    - Date of expected or booked follow up patient visit
6. The patient's medical chart itself might be flagged in some way to aid this tracking
7. It can sometimes be difficult to contact a patient by telephone, and sometimes they do not attend planned follow up appointments:
    - The number and intensity of efforts to reach the patient by telephone should be proportional to the severity and urgency of the medical problem. All attempts to contact the patient should be documented.
    - If the patient fails to attend an appointment, or you have been unable to speak to them directly about test results which raise a clinical concern, then send a letter to the patient advising them of the action they should take
8. If you order investigations it is your responsibility to review, interpret and act on the results. If you go off duty before the results are known, you should alert the incoming doctor that there are results outstanding. Furthermore, you should check the results when you are next on duty.

Applying the Cole's principles to general practice

The Cole's principles offer a structure to develop personal and practice policies for managing test results. In reality, however, there are many situations where uncertainty exists despite these guidelines. Being aware of the issues which may arise and considering how best to respond in the interests of both the patient and the clinician is beneficial. Time and resource constraints make managing test results a delicate balancing act, but it is vital there are processes in place to ensure patients receive the safest and best possible care.

A practical approach to the management of test results is to first consider whether the test is necessary, and then if the clinical decision is made to proceed with the test, explain the test to the patient, discuss how they would prefer to receive

the results and when the results are expected. The clinician who ordered the test is then responsible for ensuring that they (or a delegated colleague) receive the results, convey these results to the patient and undertake any necessary follow up.

The two key factors are:

1. **Effective communication with both patients and medical colleagues**
2. **Clear lines of responsibility**

First consider if the test is needed

Before requesting a laboratory investigation, the clinician should consider the expected benefits of knowing the test result and then decide if the test is still necessary.

Considerations before ordering a test:

- What is my reason for requesting this test?
- Has this test already been done? Does it need to be repeated?
- Will the test improve patient (or in some cases, family or partner) care?
- Is this the right test or combination of tests for the clinical situation?
- Is it the right time to do the test?
- How will the test result be interpreted?
- How will the test result influence patient management?
- What will be the consequences of a false positive result?
- Are there potential harms of doing this test?

For further information, see: "Best Tests? The general principles of laboratory investigations in primary care", Best Tests (Feb, 2013).

Communicating with the patient

Once the clinical decision has been made to request a test, the next step is to ensure that the patient agrees to the test, understands why the test is being requested, what condition/parameter is being tested for and the aim of the test, e.g. to confirm or exclude a suspected condition. The clinician and patient then need to discuss how the results will be given, the expected time frame for the results and what form the results will take, e.g. a positive/negative result or a numerical value.

This shared decision making approach improves health literacy, and enables the patient to take a more active role in their care. The patient will know when the results are expected, and can contact the practice if they have not received their results or if their condition changes.

Patient rights and informed consent

Under the 1994 Health and Disability Commissioner Act, patients have the right to be given information about their health or disability, the service being provided, the names and roles of the staff involved as well as information about any tests and procedures required and their test results.[4]

Patients have the right to be notified of **all** test results and should be given their results if they ask for them.[1] If it is practice policy to only inform patients about clinically significant results, this should be explained to the patient and their consent obtained (for not reporting on normal results).[1]

Many practices will have a policy regarding notification; a pamphlet that explains this can be a useful way to back up verbal discussion of this policy.

Issues to consider when informing patients of results:

- Regularly check that phone numbers are up to date in the patient's record
- To manage workload, practices may specify times that the practice nurse is able to be called for results. The full responsibility for this should not, however, be left up to the patient, and the practice should have a system of identifying when results have not yet been given to the patient.
- Have an agreement with the patient as to whether a voice mail message about their results can be left if they are unavailable or if they consent to a family member being informed; relevant issues include ensuring confidentiality and that the patient has received the result
- Text messaging or emailing may be considered as an option for delivering routine test results; relevant issues include ensuring confidentiality, and accuracy with written results

The introduction of electronically accessible health records into the New Zealand healthcare system ("patient portals") is likely to influence the way that patients interact with clinicians, including how they receive test results.

Delivering bad news

In many situations, the clinician will anticipate when a result is likely to be serious, and will have already made an arrangement with the patient to return for a follow-up consultation in which they can receive their results, or will have already prepared them for receiving the news.

Unexpected bad news is often more challenging to deal with as the patient has not necessarily been prepared for this. Patients may feel extremely anxious if they are asked to return to the practice for their results, especially if it has been suggested that they bring a support person.

Ideally, any result which has the potential to be serious should be informed to the patient in person, although financial and time factors may be a barrier to this for both the patient and practice. This is a decision that is likely to be made on a case-by-case basis.

What to do when the patient is difficult to contact

The Health and Disability Commissioner (HDC) considers that it is the clinician's responsibility to contact patients with significant results, even when the patient has delayed, cancelled or not attended the follow-up consultation.[1]

It is good practice to document all attempts to contact the patient in their medical records. If repeated attempts fail consider other ways of contacting the patient depending on the urgency of the clinical situation, e.g. if the result is non-urgent a letter could be sent to the patient advising them of the test result and the suggested course of action.

Ensure that patient records are regularly updated with multiple contact options.

"Managing the responsibility of test results is a balance between autonomy, efficiency and reliability; too much of one takes away from the others. It is difficult to get all three aspects balanced".

– Dr Steve Searle, General Practitioner

Communicating with other health professionals

It should be the responsibility of the clinician who has ordered the test to ensure that the results are reviewed, the patient is informed and any necessary action is taken.[1]

This can mean that the clinician themselves undertakes this role, or that they take responsibility for delegating this to someone else. An effective electronic management system is also an essential part of this process (see opposite: "Have overdue results been identified and followed up?").

Once a test has been requested, responsibilities include:

- Following up the result in the expected time frame
- Following up with the patient if they have not presented for the test (relying on a system that can identify this)
- Ensuring the patient has been notified of their results
- Discussing with the patient the intended course of action in response to the test result, e.g. a repeat or additional investigation, a change of medicine or reassurance; this should be documented in the patient's notes
- Referring the patient to another provider if necessary on the basis of results received
- Forwarding results, particularly abnormal results, to other providers involved in the patient's care, as appropriate
- **Arranging for urgent test results to be followed up after hours**; contact details of the clinician who will follow up the result and the patient's contact details should be included on the request form in case the result requires urgent action. Practices may have a "last resort" arrangement with the local after hours service if they are unable to provide an after hours contact.

The following scenarios may add complexity to the usual practice protocol for following up tests:

When an "after hours" clinician or locum is providing cover

A frequently encountered issue in regards to responsibility for test follow up is clinicians ordering tests for patients who are not usually in their care, e.g. clinicians working in an after hours service. If possible, tests may be deferred until the patient is able to consult with their usual General Practitioner. If this is not possible, the clinician who ordered

the test should provide clear instructions on who is expected to follow up the result.

When a locum is providing cover in a practice, best efforts should be made to ensure that they are aware of the systems the practice has in place to manage test results. "Handover" should ideally occur in regards to patients with outstanding results that will need to be followed up. If a face-to-face handover is not possible, a written summary can be provided or the task system on the PMS can be used to note any follow up that is required. It is reasonable to assume that locums have the same responsibilities with regard to following up test results as the usual clinician they are providing cover for.

When the practice has part-time clinicians or clinicians go on leave

Practices are encouraged to have a system in place for managing results of tests ordered by clinicians who work part-time. Some clinicians will access results from off-site, however, this should not be relied upon when the clinician is not on call. A "buddy system" where a colleague agrees to review the results of another can help to ensure that urgent results are attended to promptly when the clinician is away from the practice. This system also relies on effective communication between clinicians as to what follow up has occurred and what course of action has been agreed to with the patient.

A similar scenario is when clinicians order a test and are not working at the practice again until after the results are expected, or take planned or unexpected leave. Practices should have a plan in place for hierarchy of responsibility in this situation.

"Managing test results for a busy clinician can be difficult. Standards of care have changed considerably over the last 20 years and efficient, effective methods of coping with test results are now expected. Many clinicians now use the concept of 'Protected time' to undertake tasks such as going through the 'inbox' and doing repeat prescriptions; time in which there will be no interruptions to tasks with considerable safety implications."

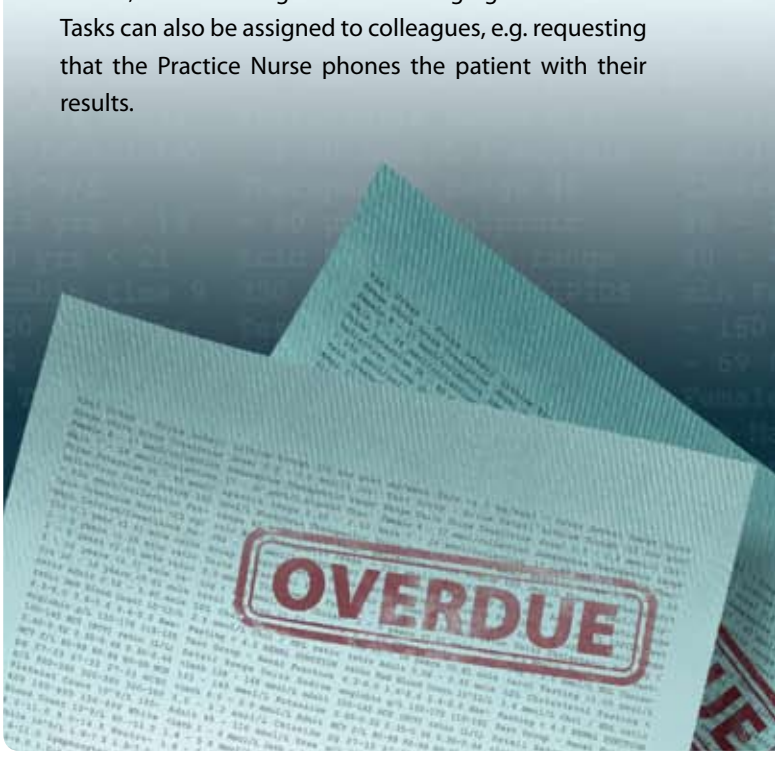
– Dr Steven Lillis, General Practitioner

Have overdue results been identified and followed up?

Failure to follow up on abnormal or overdue test results is a global patient safety concern. Practices should ensure that the tracking system they use for test results is effective in identifying results which have not been read or actioned. In addition, there needs to be a system in place for identifying patients who have not presented for tests that have been requested.

Any system is not 100% fail-safe, however, there are some strategies that can reduce the risk of missed test results. This includes having standard practice procedures for following up results, including tests which have not taken place, optimal use of the computer-based practice management system (PMS), having an audit system in place to check how the process is performing and using a shared decision-making approach so the patient also takes responsibility in presenting for tests and following up results.

Some PMS have the ability to set task reminders that alert the clinician when a particular result has not arrived back into their results inbox, when they need to follow up a result or if a patient has not presented for a test. This can provide an excellent easy way to track results, from ordering a test to managing the outcome. Tasks can also be assigned to colleagues, e.g. requesting that the Practice Nurse phones the patient with their results.



When clinicians work at multiple practices

Occasionally results that arrive in the practice are unmatched to a patient. There are several possible reasons for this, e.g. the details of the patient have been entered incorrectly or they are no longer registered at the practice. However, the reason may be that the results have been forwarded to the correct clinician, but the incorrect location, e.g. a General Practitioner who works part-time hours at two different practices.

If results are received for patients not registered to the practice, check if they might be patients at other practices that the clinicians cover. Where possible, forward results to the correct location, and confirm that they have been received. Alternatively, contact the laboratory to report the error.

When copied in to test results ordered by other clinicians

When multiple clinicians are copied in on a request form for a test, results will be sent to each clinician. This can create a particular risk of error if it is unclear who has responsibility for following up results and whether follow up has occurred. It needs to be made very clear who is responsible for following up the test results. Although best practice is for the clinician who ordered the test to be responsible for following up the results, this may not always occur. For example, if a test has been ordered from an after hours clinic and the result is not urgent, it may be assumed that the patient's usual doctor, who is copied into the results, will follow this up.

Unless communication has been received about who is responsible, clinicians who have been copied in to test results should double check that the result has been actioned and the patient has received appropriate follow up. One way to avoid confusion about responsibility for following up results is instead of copying other clinicians in to results, they can be informed about the results (if necessary) in an email or letter.

A common scenario is for primary care clinicians to be copied in to multiple results from tests performed on patients in secondary care, or to be sent instructions to follow up tests, or request additional tests, in a discharge letter. Often the primary care clinician will be unaware of the clinical situation regarding the patient, and they may not have been seen in the general practice for several years, and may even be no longer registered with the practice. It is then very difficult to take responsibility for following up results. In addition, the clinician may feel hesitant to counsel a patient about a result or undertake further investigations when they are uncertain about the clinical context. Responsibility may extend to informing the secondary care clinician who ordered the test that follow up will not be undertaken (or that further information is required).

In Summary: Checklist for managing test results

1. Was the test needed?
2. Was it the right time for the test?
3. Was the most appropriate test ordered?
4. Was it explained to the patient why the test was ordered?
5. Was there a clear understanding with the patient as to when they would receive their results and in what circumstances, e.g. significant or abnormal results only?
6. Was there a discussion with the patient about how they would prefer to receive their results?
7. Was it clearly defined who was responsible for following up the test result and explaining the result to the patient?
8. Were the results received in the expected timeframe? If not, were they followed up?
9. Was the patient informed of their results in a timely manner?
10. Did appropriate clinical follow up occur based on the test result?

Rapid response: comment on this article online at:
www.bpac.org.nz/BT/2014/August/testresults.aspx

"I receive literally hundreds of tests copied in from the hospital. I often do not know the clinical situation, and often they are for patients who have not attended the practice for five or more years. These usually originate from ED or a particular hospital clinic. Sometimes there is a letter 'GP to chase up results'. This takes an enormous amount of time and effort for absolutely no return. These patients are usually not enrolled in the practice. I would argue very strongly that they are not my responsibility."

– Dr Jim Reid, General Practitioner

Case reports: lessons to be learnt

The following examples are based on real cases in which communication break-down in regards to responsibility for test results compromised patient safety.

N.B. These reports were received via the bpac^{nz} patient safety incident reporting system, which is currently inactive.

Case report 1: lung cancer diagnosis missed

A patient with a history of COPD presented at an after hours clinic, with a suspected chest infection. The patient was advised to return the next day for a chest x-ray to exclude pneumonia. A pulmonary nodule was detected on x-ray and it was recommended that the patient undergo a CT scan for further assessment. The result was phoned through to the Clinical Leader at the after hours clinic by the Radiologist. The Clinical Leader sent a note to the patient's named General Practitioner advising that follow-up was required. The General Practitioner had not seen the patient for ten years and did not receive the letter from the Clinical Leader, but did receive the x-ray report. The General Practitioner, after seeing the result had been telephoned, assumed that the after hours clinician who ordered the x-ray was taking responsibility for patient follow up. The patient changed General Practitioners shortly afterwards and the report was faxed to the new practice. The new practice assumed the previous General Practitioner had actioned follow up. The patient presented to the new General Practitioner one year later with a persistent cough. A repeat chest x-ray was requested and it showed a large tumour.

This case report shows how adequate follow up can be missed when one clinician assumes that another has taken action on test results. Each of the three clinicians assumed that one of the other two was taking responsibility to follow up the original x-ray. However, there was no successful contact between clinicians that may have resulted in earlier diagnosis and treatment.

Case report 2: practice communication fail

An abnormal laboratory result for a patient was notified to a General Practitioner by phone one evening when they were away from home for a few days. The General Practitioner decided the result needed to be actioned the next day and informed the laboratory to fax the result to the practice as per usual procedure, with the intention it would be viewed by another clinician the next morning.

The General Practitioner made three phone calls to the practice the next day to follow up:

- Call one – could not get through to the practice
- Call two – left a message on the lead clinician's mobile
- Call three – left a message on the nurse's answer phone

Upon returning to work two days later, the General Practitioner noticed the faxed result, which had been scanned by a receptionist but not viewed by a clinician. A family member of the patient had also phoned the practice and spoken to a nurse, but this conversation had not been properly documented. The first nurse's phone was found not to be working and the lead clinician had not checked their phone message. The patient was urgently admitted to hospital for treatment.

This reveals how patient follow up can be delayed when messages are missed due to breakdowns in communication. It also highlights potential problems when the clinician who ordered the test is away from the practice when the results are received. It shows how important it is that information is relayed directly between clinicians and other practice staff. Would a 'handover' prior to going on leave, to delegate responsibility for follow up to another clinician, or an electronic task reminder in the PMS for the practice staff have changed the outcome for this patient?

ACKNOWLEDGEMENT: Thank you to **Dr Steven Lillis**, General Practitioner, Hamilton and Medical Advisor, Medical Council of New Zealand for expert review of this article.

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The New Zealand Laboratory Schedule and Test Guidelines: haematology tests

The New Zealand Laboratory Schedule has been created to provide consistent guidance and ensure uniform availability of tests across all District Health Boards (DHBs). The new Schedule divides tests into Tier 1 and Tier 2 to indicate whether all referrers can order the test, i.e. Tier 1, or whether a test must be ordered in conjunction with another health professional with a particular area of expertise, i.e. Tier 2. In addition, clinical guidelines are provided on the use of some tests. In this article we focus on the haematology tests in the schedule.

It is estimated that 85% of clinical decisions involve laboratory investigations. The objective of the New Zealand Laboratory Schedule is to make the most relevant tests available, and to provide guidelines on their optimal use.

The schedule was created by an overall steering group, managed by DHB Shared Services, with subgroups formed for each area of clinical speciality. The haematology subgroup is led by Dr Stephen May and made up of clinical and laboratory haematologists, with representation from around the country. The subgroup continues to meet to consider new investigations available as well as reviewing indications for older tests.

The haematology tests are ranked in Tier 1 and Tier 2 tests

Tier 1 tests may be requested by any registered medical practitioner as well as other practitioners who are able to request investigations, e.g. midwives.

Tier 2 tests are specialist tests whereby the referrer needs appropriate vocational registration or credentialing to order the test. Tier 2 test are also able to be ordered by General Practitioners on the advice of a relevant specialist.

Guidelines on selected haematology tests

Erythrocyte sedimentation rate (ESR) (Tier 1)

ESR has historically been used in clinical medicine as a measure of inflammation. However, it has significant limitations in terms of measurement accuracy. In addition, ESR is affected by numerous physiological variables and by factors other than inflammation, such as haemoglobin and plasma protein levels.

Despite its limitations, ESR may have some advantages in the assessment of the following conditions:

- Systematic lupus erythematosis
- Rheumatoid arthritis
- Kawasaki disease
- Rheumatic fever
- Hodgkin lymphoma
- Temporal arteritis
- Inflammatory bowel disease in children (initial assessment)

ESR should not be used to screen for plasma cell dyscrasias. If these conditions are suspected, protein electrophoresis and immunofixation or serum free light chain assays (see below) should be used.

C-reactive protein (CRP) is the preferred investigation for the assessment for a possible inflammatory or infective disorder. It is seldom appropriate for both ESR and CRP to be requested together.

While ESR and CRP are no longer routinely requested together for most conditions, either marker (or both) can be raised in giant cell arteritis (temporal arteritis) and given the significant potential for morbidity in people with giant cell arteritis, it is recommended that both are requested in the initial presentation. For further information see: "Giant cell arteritis: Always keep it in your head", BPJ 53 (Jun, 2013).

Serum free light chains (Tier 2)

The symptoms of multiple myeloma may be classical (e.g. bone pain) or non-specific. If multiple myeloma is suspected, a practical approach is to first request serum protein electrophoresis. If an increase in immunoglobulins is found, or the test is normal, but clinical suspicion remains, the need for further testing should be discussed with a Haematologist or other relevant specialist.

Serum free light chain assays can detect elevated levels of light chains (of immunoglobulin) in the blood, even when those levels are undetectable by serum protein electrophoresis. In a serum free light chain assay, both free kappa (κ) and lambda (λ) chains are measured and the ratio is calculated. Excessive free κ or λ increases the likelihood a of monoclonal plasma cell disorder.

The International Myeloma Working Group guidelines suggest that a serum free light chain assay is used for prognostic purposes in all patients with:

- Monoclonal gammopathy of unknown significance (MGUS)
- Smouldering multiple myeloma
- Active multiple myeloma
- Amyloidosis

The test is also indicated for patients with:

- Suspected myeloma, MGUS or amyloidosis
- Unexplained renal impairment
- Unexplained proteinuria
- Unexplained peripheral neuropathy

Follow-up testing is recommended no more frequently than every three months, unless the patient is on active chemotherapy.

For further information see: "Making sense of serum protein bands", Best Tests (Jul, 2011).

Chronic lymphocytic leukaemia (CLL) investigations (Tier 1)

Early B-cell chronic lymphocytic leukaemia is the most common type of adult leukaemia. It mainly affects people aged over 50 years (median 65 years), and patients are asymptomatic in the early stages with the only feature being a peripheral lymphocytosis. Diagnosis of chronic lymphocytic leukaemia (CLL) is based on cell marker studies (flow cytometry), along with clinical assessment.

Consider CLL or other lymphoproliferative disorders if the patient has persistent lymphocytosis of $> 5 \times 10^9$/L for more than three months.

1. Discuss with the Haematologist if cell marker studies are required for persistent unexplained lymphocytosis
2. Refer to the Haematology Outpatient Department if the referral criteria are met (see below); this usually signals advanced or progressive disease. Otherwise, regular monitoring (full blood count) in general practice is indicated; initially every three to six months, then yearly if stable or slow.

Referral criteria are outlined in full in the Laboratory Test Guidelines. The criteria include:

- Age < 55 years, with progressive disease
- Significant symptoms, e.g. significant weight loss, fatigue, night sweats
- Advanced stage of disease
- Disfiguring lymphadenopathy or hepatosplenomegaly
- Recurrent infections
- Haemolytic anaemia
- Lymphocyte count which has doubled in less than six months and is $> 30 \times 10^9$/L

Haemoglobinopathy investigations (Tier 1)

The most significant haemoglobinopathies/thalassaemias are: sickle cell disease, beta thalassaemia and alpha thalassaemia ("CIS" inheritance pattern). Although there are currently no specific referral criteria on the laboratory schedule for patients suspected of having one of these conditions, discussion with a Haematologist is recommended.

There is no formal haemoglobinopathy screening currently undertaken in New Zealand, therefore investigations are done on an *ad hoc* basis (as a once only investigation) for:

1. Investigations of hypochromic microcytic blood pattern when iron deficiency has been excluded
2. High risk ethnic groups, e.g. Middle Eastern, African, Pacific peoples
3. Follow up of family studies
4. Investigations of abnormal haemoglobins during other investigations, e.g. an abnormal haemoglobin found incidentally while testing HbA_{1c} for diabetes

For further information on investigating haemoglobinopathies/thalassaemias in patients with microcytic anaemia, see: "Anaemia on full blood count: investigating beyond the pale", Best Tests (Sep, 2013).

Inherited thrombophilia testing (Tier 1 and 2)

Thrombophilia testing is of limited utility and should not be used as a screening test. However, it is indicated in the following situations:

- Idiopathic venous thromboembolism in patients aged less than 45 years
- Warfarin induced skin necrosis
- Children presenting with purpura fulminans
- Siblings of patients with homozygous factor V Leiden
- Homozygous PT20210A or compound heterozygotes for these mutations
- Thrombosis in unusual sites, e.g. cerebral, mesenteric or portal

In all other situations testing should only be undertaken after consultation with a Haematologist or as part of a clinical trial.

The need for any investigation is dependent on the usefulness of the result and if there will be no change in clinical management as a result of the investigation, then it is not indicated.

For further information, see: Baglin T, Gray E, Greaves M, *et al*. Clinical guidelines for testing for heritable thrombophilia. British Journal of Haematology 2010;149:209-20.

Additional considerations for testing

Any testing should be requested as a result of, or to provide evidence of, a clinical condition, or to monitor chronic conditions or exclude clinically significant differential diagnoses.

Tests on the Laboratory Schedule should not be used for screening purposes outside a formal screening programme. Pre-employment screening is excluded from funding, as is testing for immigration purposes, or tests required prior to travel, although these tests can be purchased from an IANZ accredited laboratory.

The Laboratory Test Schedule and Laboratory Test Guidelines are available from: **www.dhbsharedservices.health.nz/Site/Laboratory/Default.aspx**

ACKNOWLEDGEMENT: Thank you to **Dr Stephen May**, Clinical and Laboratory Haematologist, Clinical Director Pathlab and Chair of the Haematology Subgroup, New Zealand Laboratory Test Schedule and Guidelines for contributing to this article.

Investigating

myalgia in patients taking **statins**

Muscle pain (myalgia) and weakness is experienced by up to 10% of patients taking statins. However, myalgia is commonly experienced by all people at some stage in their life, regardless of statin use. To avoid the unnecessary withdrawal of statin treatment, a systematic approach to the investigation of muscle symptoms in patients taking statins is advised. Routine laboratory monitoring for statin-associated adverse effects is not recommended in asymptomatic patients.

Part one: Safe and effective use of statins

Statins are among the most widely prescribed medicines in New Zealand; in 2013, approximately 500 000 patients were dispensed a prescription for either simvastatin or atorvastatin.[1] Alongside lifestyle modification, statins are the mainstay of lipid management. New Zealand and international guidelines recommend statins for the primary prevention of cardiovascular disease (see: "Guidelines for use of statins", over page.[2, 3, 4] Numerous trials have confirmed that statin treatment is effective in the secondary prevention of cardiovascular events caused by atherosclerosis. Among patients with heart disease who take statins for five years, the number needed to treat (NNT) to prevent one non-fatal myocardial infarction is 39, and the NNT to prevent one death is 83.[5]

Before a patient begins taking statin treatment it is important that causes of dyslipidaemia are considered and managed appropriately, e.g. high saturated fat diet, excessive alcohol consumption, hypothyroidism, diabetes, liver disease, nephrotic syndrome and corticosteroid treatment.[4]

Monitoring lipid profile in patients taking statins

It is recommended that once a patient is initiated on statin treatment that their lipid profile should be monitored every three to six months, until their levels are stable, and then no more than once a year.[4] Measuring lipid levels more frequently may produce misleading results as day-to-day variation can be greater than trends over time.[4]

Low-density lipoprotein bound cholesterol (LDL-C) levels are widely used as an indicator of lipid management in patients taking statins.[6] When given at comparable doses the ability of the various statins to reduce LDL-C is similar.[7] There is no specific target LDL-C in patients with a five-year cardiovascular risk less than 20%; the aim is to achieve a moderate reduction in LDL-C.[4] The intensity of statin treatment is dependent on the patient's cardiovascular risk. A greater reduction in LDL-C from baseline should be expected in patients with a cardiovascular risk greater than 20%.[2]

Monitoring statin safety is not routinely required

Statins are generally considered a safe class of medicine, however, adverse effects are sometimes reported. These adverse effects can be grouped into the "Five Ms":[8]

1. Muscle symptoms, e.g. myalgia and/or weakness
2. Medicine interactions
3. Major organ effects, e.g. hepatic and renal effects
4. Metabolism, i.e. risk of type 2 diabetes
5. Memory, i.e. cognitive adverse effects

Most guidelines suggest taking a baseline measurement of liver function (alanine aminotransferase – ALT) before initiating statin treatment. However, to avoid unnecessary testing, it is suggested by many New Zealand experts that this approach be limited to patients in whom there is reason to suspect liver dysfunction (see over page).

Baseline testing of muscle enzymes (creatine kinase) prior to statin treatment is unnecessary, unless there is a specific reason to do so, e.g. the patient has risk factors (See: Investigating Myalgia, Page 18).

Once treatment has started, monitoring of ALT or creatine kinase is unnecessary unless clinically indicated, i.e. the patient is symptomatic or has specific risk factors.

Guidelines for initiating statins

In the latest update of the New Zealand Cardiovascular Risk Assessment guidelines (2013) it is reinforced that cardiovascular management options should be discussed with patients. It is also recommended that a more graded approach to the intensity of management be taken that reflects the patient's combined cardiovascular risk.

For patients with:[4]

- A five-year cardiovascular risk less than 10% – lifestyle measures are used to manage their cardiovascular health
- A five-year cardiovascular risk of 10 – 20% – a shared decision making approach should be taken when considering the benefits and harms of pharmacological treatment, including statin initiation. Following lifestyle management, patients are recommended to have their lipid profile measured after six to twelve months and their cardiovascular risk recalculated. There is good evidence that statin treatment will lower cardiovascular risk in this patient group with benefit increasing as the patient's cardiovascular risk rises.
- A five-year cardiovascular risk greater than 20%, or with known cardiovascular disease – statin treatment is strongly recommended

The patient's TC:HDL-C (total cholesterol:high-density lipoprotein bound cholesterol) ratio is a powerful marker of cardiovascular risk. In patients with a TC:HDL-C ratio ≥ 8, or a TC ≥ 8 mmol/L lipid-lowering treatment is generally recommended regardless of the patient's combined cardiovascular risk.[4]

Hepatotoxicity with statins

Hepatotoxicity due to statin treatment is highly unusual. Rarely, hepatitis and jaundice are reported in patients taking statins.[9] New Zealand guidelines state that the risk of hepatotoxicity due to statin treatment appears negligible,[6] and routine monitoring of liver function is considered unnecessary.[2, 6]

United States guidelines recommend that a baseline ALT test be performed in patients prior to initiating statin treatment.[2] United Kingdom guidelines also recommend measuring liver enzyme levels within three months of starting statin treatment and at 12 months.[3] However, ALT testing is unlikely to provide useful information unless there is reason to suspect that the patient has liver dysfunction. Elevations in transaminase levels are typically seen in less than 3% of patients taking statins and are not significantly different from rates among patients taking placebo.[8] Furthermore, these elevations often return to normal without patients needing to stop taking statins.[8]

If an ALT test is requested in a patient with suspected liver dysfunction, a markedly elevated level would be considered a risk factor for adverse effects of statins, and the risk versus benefits of statin treatment should be revisited; statins should be used with caution in patients with an ALT greater than three times the upper limit of normal.[9] If the patient does decide to begin statin treatment, a lower dose may be appropriate.[8] Patients with non-alcoholic fatty liver disease will typically display a mild to moderate increase in ALT.[10] Atorvastatin has been found to reduce aminotransferase levels in patients with fatty liver disease. Mildly abnormal LFTs in a patient with non-alcoholic fatty liver disease should not be considered a contraindication for statin treatment.[10]

It is reasonable to monitor hepatic function in patients taking statins with suspected liver dysfunction and an elevated baseline ALT level, or in patients who develop symptoms suggestive of hepatotoxicity, e.g. unexplained fatigue or weakness, loss of appetite, abdominal pain, dark-coloured urine, or yellowing of the skin or sclera.[2]

Best Practice Tip: If a liver function test is requested in the context of statin treatment, request an ALT test only, rather than "LFTs". Further testing of liver function can be performed by the laboratory on the same blood sample if necessary, within a limited time period. Also consider customising your PMS so when requesting investigations, individual liver function tests can be selected rather than "LFTs".

Monitoring for other adverse effects in patients taking statins

Acute kidney injury

The risk of acute kidney injury (AKI) occurring in patients taking statins is slightly increased. It is likely that this is at least in part due to muscle protein entering the blood stream. A large study of over two million patients aged over 40 years who were recently initiated on statins found that the risk of people without chronic kidney disease (CKD) being hospitalised due to AKI was increased by approximately one-third during the first 120 days of high potency (≥ 40 mg daily simvastatin) statin treatment, compared to patients receiving low potency statins.[29] However, the absolute risk of this occurring was small and it was estimated that 1700 patients would have to be treated with high potency statins for four months to cause one additional hospitalisation due to AKI.[29] Interestingly, it was found that patients with CKD who were receiving statin treatment were not at an increased risk of AKI.[29] This unexpected result has caused some researchers to interpret this study with caution. Patients can be advised that the risk of AKI due to statin treatment is exceedingly low. Monitoring of kidney function is a routine part of care in patients at risk of AKI, e.g. older patients or patients taking long-term NSAIDs, however, monitoring kidney function to specifically detect statin-induced renal impairment is not necessary.

For further information see: "Statins and the risk of acute kidney injury", BPJ 52 (Apr, 2013).

Type 2 diabetes

Patients taking statins have an increased risk of developing diabetes that increases according to treatment intensity.[2] For statin treatment described as moderate intensity (simvastatin 20 – 40mg daily), for every 1000 patients approximately one extra patient will develop diabetes per year; in patients taking high-intensity statins there will be approximately three extra cases of diabetes.[2] However, the risk of new-onset diabetes in people taking statins with elevated cardiovascular risk is outweighed by the reduced risk of cardiovascular events in most patients with type 2 diabetes; except for those aged under 40 years, those aged over 75 years and those with low LDL-C for whom treatment decisions should be individualised.[2] In adults with diabetes, some of whom had coronary heart disease, statin treatment is reported to decrease the relative risk of cardiovascular events by 20%.[2] Furthermore, the people who are at most risk of new-onset diabetes are those who are most likely to gain benefit from the use of statins. The patient's HbA_{1c} level from their most recent cardiovascular risk assessment will serve as a baseline for regular monitoring for type 2 diabetes. All patients taking statins should continue to have their HbA_{1c} levels regularly tested each time a cardiovascular risk assessment is performed.[2] If a patient does develop diabetes they can be advised to continue statin treatment and be further encouraged to maintain a healthy lifestyle.[8]

Memory

There is no clear evidence that statins have an adverse effect on memory, despite there being observational data of a link between statins and memory loss and confusion.[8] There are also case reports of cognitive decline in patients taking statins that has resolved with switching or stopping statin treatment.[8] However, two large randomised trials (the Heart Protection Study and the PROSPER study of statin use in older patients) did not detect any significant difference in the rate of cognitive decline in patients taking statins versus placebo.[8] An early meta-analysis of observational studies even suggested that onset of cognitive decline could be delayed with the use of statins, possibly by decreasing the risk of cerebral infarcts.[8] Switching to a different statin, taking a low dose of a statin, or trialling alternate day dosing are possible strategies for treatment in patients with an elevated cardiovascular risk who are concerned about any cognitive effects of statin treatment. Patients can be reassured that if they do experience any cognitive symptoms due to statin use that these are likely to resolve within three to four weeks of stopping treatment.[8]

Part2: Investigating Myalgia

Myalgia is a potential adverse effect of statin treatment

Myalgia, with or without muscle weakness, is the most common adverse effect associated with statin use, and is reported to occur in up to 10% of people prescribed statins.[11] Statins are not necessarily the cause of myalgia in all of these people, however, as myalgia is frequently reported in the general population and can have many aetiologies.

Myalgia may be described as a muscular ache, heaviness, stiffness or cramping sensation; tendon pain and nocturnal leg cramps may also occur.[12] Muscle weakness can also occur without discomfort and may be noticed by patients as an inability to open jars, difficulty snapping their fingers or difficulty getting out of a chair.[12] Statin-associated myalgia is characterised by the symmetrical involvement of large and proximal muscle groups, in particular the legs.[13] Symptoms typically begin within six months of initiating the statin.[13]

When myalgia is associated with muscle inflammation, this is referred to as myositis. Myositis is usually accompanied by an elevation in serum creatine kinase.[12] Rhabdomyolysis occurs when the inflammation is associated with muscle fibre break-down, releasing myoglobin into the bloodstream.[13] The distinction between myositis and rhabdomyolysis is not always clear, however, a broadly accepted criteria for rhabdomyolysis is serum creatine kinase levels more than ten times the upper limit of normal, with evidence of myoglobinaemia.[8, 11, 13] Other definitions of rhabdomyolysis include elevations of creatine kinase greater than 40 times the upper limit of normal, and increased creatine kinase in association with renal failure.[14]

Elevations of creatine kinase are not necessarily diagnostic of a pathological process. Transient elevations can occur in healthy people, e.g. following vigorous exercise. Serious complications of muscle cell damage are more likely to occur in patients with risk factors, such as co-morbid illness, dehydration or pre-existing renal impairment. These complications include acute kidney injury (AKI) and widespread vascular coagulation.[12] Death due to rhabdomyolysis in patients taking statins is extremely rare; more than eight thousand patients would need to take a statin for at least 40 years for one extra death to occur.[15]

A recent study assessing the Effect of Statins On Skeletal Muscle Function and Performance (STOMP) involved giving high dose atorvastatin (80 mg), daily, to over 200 healthy females with no history of statin use, for six months.[16] It was found that the average creatine kinase level in females taking a statin increased by 20.8 U/L, compared to placebo.[16] The normal creatine kinase range is 30 – 180 U/L for females and 60 – 220 U/L for males.[17] Nineteen patients taking atorvastatin reported myalgia, compared to ten taking placebo, but there was no noticeable difference in terms of muscle strength, e.g. hand-grip, elbow flexor and knee extensor strength.[16] A lower incidence of myalgia is reported in clinical trials than is experienced by patients taking statins in clinical practice possibly due to the exclusion from studies of patients with a history of muscle symptoms, or risk factors for the development of myalgia.[8]

The pathophysiology of statin-associated myalgia

Multiple mechanisms are thought to contribute to the development of statin-associated myalgia, and no one mechanism fully explains muscle symptoms associated with statin use:[12]

- Cholesterol plays an important role in maintaining cell membrane function. Disruptions to cholesterol synthesis may affect membrane ion channels and thereby modify muscle membrane excitability. This effect has been observed in some animal models. However, inhibitors of squalene synthase (involved in the final step in cholesterol synthesis) also lower cholesterol, but do not cause muscle damage.
- Mevalonate is a precursor of co-enzyme Q10 (CoQ10 or ubiquinine), as well as being a precursor of cholesterol, and is also an important antioxidant involved in the electron transport chain in mitochondria. Reductions in CoQ10 have been suggested to interfere with cellular respiration and result in muscle toxicity. However, muscle CoQ10 levels do not correlate well with histological changes.[11] There is insufficient evidence to recommend the routine administration of CoQ10 for the prevention of statin-associated myalgia.[18]
- Statins may cause a reduction in other synthetic precursors of cholesterol, which have functional roles in cellular protein physiology
- Programmed cell death (apoptosis) in skeletal muscle may be triggered by statins
- Statins have been shown to decrease muscle strength by altering the movement of calcium within animal muscle cells

Risk factors for statin-associated myalgia

Myalgia is more likely to be experienced in patients taking statins, if they have additional risk factors (Table 1). For example: frail, elderly females; people with co-morbidities such as chronic kidney disease and diabetes; people taking high doses of statins or medicines which interact with statins; and people with a genetic pre-disposition.[13]

Medicine interactions

The risk of patients experiencing myalgia when taking statins metabolised by the cytochrome P-450 (CYP) 3A4 system, e.g. simvastatin and to a lesser extent atorvastatin, is increased if they are taking other medicines that also interact with the CYP 3A4 system, e.g. macrolide antibiotics.[19] A study investigating over 3000 cases of statin-associated rhabdomyolysis found that in more than half of cases, patients were also taking medicines known to affect statin metabolism.[19]

Table 1: Risk factors for statin-associated myalgia, adapted from Ahmad 2014[13]

Patient characteristics	■ Age over 80 years ■ Female ■ Ethnicity: people of African and Caribbean descent are reported to have a substantially increased risk of statin-associated myalgia compared to people of European descent.[12] People of Asian ethnicity have an increased risk of developing adverse effects following treatment with rosuvastatin.[13] It is unknown if there are ethnic differences in the incidence of statin-associated myalgia among Māori and Pacific peoples. ■ Small body size and frailty ■ Excessive physical activity ■ Drinking more than 1 L of grapefruit juice per day ■ Personal or family history of muscle symptoms ■ History of elevated creatine kinase levels ■ Unexplained muscle cramps
Co-morbidities	■ Hypothyroidism ■ Chronic kidney disease ■ Diabetes (type 1 and 2) ■ Alcoholism ■ A history of major surgery or a recent procedure ■ Infections
Medicines	■ High-dose statins, in particular simvastatin ≥ 80 mg, daily.[14] (although this dose is not recommended) ■ Medicines that interact with statins, e.g. macrolides ■ Concurrent use of oral corticosteroids: increases the risk of developing muscle complications by three-fold in females and two-fold in males.[22] ■ Substance use
Genetics	■ Inherited muscle diseases, e.g. McArdle disease, myoadenylate deaminase deficiency and Pompe's disease ■ Polymorphisms in CYP (P450) isoenzymes ■ Polymorphisms in drug transporter genes (see: "Genetic testing for statin-associated myalgia" Page 20)

It may be necessary to temporarily stop simvastatin if patients are required to take the following medicines:[20]

- Erythromycin and clarithromycin
- Azole antifungals, e.g. itraconazole, posaconazole and voriconazole
- Protease inhibitors, e.g. ritonavir, telaprevir, boceprevir
- Gemfibrozil
- Ciclosporin
- Danazol

Atorvastatin should also be avoided, if possible, in patients taking any of the above medicines, but if the combination is required then it should be used with caution and the patient advised to report any muscle symptoms.[20] There have been case reports of rhabdomyolysis occurring in patients taking simvastatin and azithromycin or roxithromycin, however, no clinically significant interactions are known to occur between these antibiotics and atorvastatin.[20]

New Zealand guidelines recommend a maximum daily dose of simvastatin of 20 mg for patients taking amiodarone, verapamil, diltiazem, nicotinic acid > 1 g/day, and amlodipine.[4, 9] The dose of simvastatin should be limited to 10 mg/day if given with bezafibrate.[9] Dose reductions of simvastatin should be considered for patients taking systemic fusidic acid or terbinafine, or colchicine if the patient has renal impairment.[4] Atorvastatin should be used with caution in patients taking these medicines and the patient advised to report any muscle symptoms.[20]

Pravastatin is mainly cleared by the kidneys and is a fully subsidised alternative statin for patients taking medicines that may interfere with the CYP enzyme system. The combination of pravastatin with fibrates is associated with an increased risk of muscle damage.[21]

Rosuvastatin is largely metabolised by another enzyme system (OATp1B1) and therefore has fewer and different interactions than statins metabolised by the CYP 3A4 system.[8]


For further information see: "Simvastatin and atorvastatin: beware of potential CYP3A4 interactions when prescribing other medicines", BPJ 60 (Apr, 2014).

Monitoring and investigating mylagia in patients taking statins

Laboratory monitoring for evidence of muscle damage is not routinely recommended for asymptomatic patients on a stable dose of statins for the treatment of hypercholesterolaemia.[2]

Genetic testing for statin-associated myalgia

Commercial genetic tests are available that can estimate the likelihood of some patients developing statin-associated myalgia. The test detects the presence or absence of a single-nucleotide polymorphism within SLCO1B1 on chromosome 12.[23] The polymorphism has a prevalence of 15% in the general population.[23] The risk of a person developing simvastatin-induced myalgia is increased by four and a half times with one copy of the allele, and by almost 17 times with two copies of the allele.[23] Testing is unsubsidised and has a cost to the patient of approximately NZ$120. This test may be of interest to some younger patients with high cardiovascular risk who are concerned about the possible adverse effects of simvastatin treatment and would like more information before deciding to initiate statin treatment.

Before starting statin treatment

Serum creatine kinase levels should not be routinely measured in patients prior to statin treatment, unless there are risk factors for statin-associated myalgia present (see below).[2] This is because an elevated creatine kinase level in patients without muscle symptoms does not necessarily predict the development of myalgia.[24] Creatine kinase levels up to ten times higher than normal levels have been reported to occur in patients taking statins without symptoms of myalgia.[12]

Before initiating statin treatment patients should be asked about their history of muscle symptoms, such as muscle weakness or fatigue, aching or pain, tenderness, cramps or stiffness, including frequency and duration.[2] The possible adverse effects of statin treatment should be discussed with patients and they should be instructed to report any unexplained muscle symptoms.

For patients who have an increased risk of developing statin-associated mylagia, it is reasonable to take a baseline serum creatine kinase measurement before initiating statin treatment, or alternatively, to have a lower threshold for measuring serum creatine kinase once statin treatment has begun. This includes patients with:[2]

- A personal or family history of statin intolerance
- A personal or family history of muscle disease
- Concurrent medicines that may increase the risk of myalgia
- Risk factors for statin-associated muscle damage, e.g. renal or hepatic impairment

Best Practice Tip: If testing is required, "serum creatine kinase" should be specifically requested on the form along with a note that the purpose of testing is the investigation of myalgia.

Monitoring patients during treatment

Creatine kinase levels should not be routinely monitored in asymptomatic patients taking statins.[2]

If creatine kinase levels are requested, e.g. in patients with risk factors for myalgia, and the patient is asymptomatic, but levels are markedly elevated, withdrawal and rechallenge of statin treatment may be appropriate to determine if the increase is associated with the statin.

If the patient is symptomatic, and creatine kinase levels are found to be elevated, investigate as below.

Investigating myalgia in patients taking statins

Myalgia is commonly reported in clinical trials by patients taking either statins or placebo, therefore it is important to avoid the unnecessary discontinuation of treatment.[8]

Differential diagnosis of myalgia

The characteristics of the patient's pain may help determine the degree of clinical suspicion for statin-associated myalgia:

- Myalgia associated with physical activity is likely to be self-limiting
- Acute onset myalgia with upper respiratory tract symptoms suggests viral infection
- Myalgia with swelling or localised warmth suggests localised inflammation or infection
- Myalgia in a patient with poor sleep quality and stress is suggestive of fibromyalgia syndrome, a common cause of myalgia (see: "Fibromyalgia syndrome: a constellation of symptoms", Page 23)
- Muscle pain and stiffness in the morning suggests polymyalgia rheumatica (see below)
- Slow onset myalgia with long-term symptoms is more suggestive of a chronic condition such as hypothyroidism, hypercalcaemia or severe vitamin D deficiency

Consider the possibility of other causes for the patient's symptoms and investigate as appropriate.[2] In patients who have a consistent history of muscle symptoms prior to starting their statin treatment, it is more likely that the cause of their myalgia is not associated with statin use. Polymyalgia rheumatica should be suspected in patients aged over 60 years who report shoulder and pelvic girdle pain and stiffness in the morning that improves later in the day.[25] An elevated C-reactive protein (CRP) makes a diagnosis of polymyalgia rheumatica more likely.[25] An elevated serum calcium level is suggestive of hyperparathyroidism.

For further information see: "Polymyalgia rheumatica: Look before you leap", BPJ 53 (Jun, 2013).

Red-flags: Symptoms of rhabdomyolysis

Immediately withdraw statin treatment in patients who present with myalgia and any of the following:

- Unexplained brownish-red coloured urine suggestive of myoglobinuria* (often described as "tea brown")
- Decreased urine output
- Fatigue
- Muscle weakness

The myalgia associated with rhabdomyolysis is usually severe and patients are at risk of acute renal insufficiency, which can occur when myoglobin precipitates in the urinary tubules and causes a blockage resulting in acute kidney injury (AKI).

The following tests should be requested if rhabdomyolysis is suspected:[2]

- Serum creatine kinase
- Serum creatinine
- Serum electrolytes, including calcium and phosphate
- Urine dipstick for the presence of haem, which will detect both myoglobin and haemoglobin

There is a relatively low risk of AKI in patients with a serum creatine kinase level less than 15 000 U/L, although AKI may occur with creatine kinase levels as low as 5000 U/L in patients who are older, or who also have sepsis, dehydration or acidosis.[26] If intrinsic renal damage is suspected, the patient should be referred to hospital without delay.

* Myoglobinuria can be confirmed and distinguished from haematuria, if required, by laboratory testing of a random urine sample.[2]

Ask the patient about their adherence to the statin regimen, e.g. have they recently started taking higher doses, and the use of other medicines that may influence statin metabolism. If an obvious cause of the patient's symptoms has not been identified then statin treatment should be withdrawn for at least two weeks while the patient's condition is evaluated further.[13] Recording the patient's subjective baseline score, e.g. muscle pain, on a one to ten scale, before statin treatment is withdrawn, can be a useful way of comparing muscle symptoms over time if a statin rechallenge is tried (see below).

Request a serum creatine kinase test to investigate possible muscle damage and serum creatinine to assess kidney function. However, a normal creatine kinase test does not necessarily exclude the possibility of statin-induced myalgia as biopsy-proven statin-associated muscle damage, in conjunction with muscle weakness, can occur in some patients with normal creatine kinase levels.[13] A symptom-based approach is therefore useful, supported by laboratory test results:[4]

- For patients with muscle pain, but no rise in creatine kinase, a reduction in statin dose or discontinuation of treatment may be required; monitoring of creatine kinase is not necessary.
- For patients with creatine kinase levels between three and ten times the normal level a reduction in statin dose, or discontinuation of treatment is appropriate; the patient's symptoms and creatine kinase levels should be regularly monitored if treatment is continued, e.g. weekly.
- For patients with creatine kinase levels greater than ten times the upper limit of normal, statins should be discontinued immediately

Confirming statins as the cause of myalgia

A rechallenge of the same statin at the original, or lower dose, can be used to indicate if the statin was the cause of the patient's symptoms.[2] Although the sensitivity and specificity of withdrawal and rechallenge is unknown, the STOMP trial found that 4.6% of people receiving placebo experienced myalgia during a controlled withdrawal and rechallenge.[16]

If a causal relationship is found between the patient's symptoms and statin treatment then the original statin should be discontinued.[13] At this point discuss the benefit versus risks of continued statin treatment with the patient. The adverse effects of statin treatment may outweigh the potential benefit of a reduction in cardiovascular risk provided by treatment, e.g. in frail older people. If statin treatment is reintroduced, a low dose of another statin, e.g. pravastatin, can be trialled.[2] Most of the LDL-C lowering benefit of statins occurs at lower doses.[2] The statin dose can be titrated upwards, if appropriate. Alternate day, or even twice weekly, dosing regimens have also been trialled in patients experiencing adverse effects of statin treatment.[12]

Fibromyalgia Syndrome: a constellation of symptoms

Fibromyalgia is a chronic pain syndrome consisting of a constellation of symptoms with no clear pathophysiological explanation. Fibromyalgia is a common cause of myalgia, affecting 2 – 5% of the population.[27]

Fibromyalgia can affect anyone, but occurs most commonly in young to middle-aged females.[27] The cardinal features of fibromyalgia include chronic widespread musculoskeletal pain with tenderness on examination, poor and unrefreshing sleep, fatigue and cognitive effects on short-term memory and concentration.[27] The features of fibromyalgia can therefore provide a challenge when differentiating from statin-induced adverse effects.[27]

The pathophysiology of fibromyalgia is unclear, although it is thought to occur due to long-term psychological or physical stress causing the central nervous system to alter the processing of afferent sensory input.[27] The result of these changes is that normally non-painful stimuli may become amplified and experienced as pain.[27]

The American College of Rheumatology criteria are used to diagnose fibromyalgia which involves recording the patient's pain during the previous week at different locations on their body. Sleep quality and cognitive symptoms are assessed as important features of fibromyalgia as well as the presence of headache, abdominal pain and depression.[27] Fibromyalgia is associated with stress therefore patients should be assessed for psychosocial factors causing emotional distress, muscle tension, pain and other symptoms.

Regular exercise is known to improve pain, fatigue and sleep disturbance in patients with fibromyalgia.[27] A Cochrane review found that aerobic resistance training was of particular benefit.[28] Exercise should be introduced slowly; swimming in a warm pool is a good starting point as the warm water and low resistance relieves symptoms.[27] Yoga, Qi Gong and Tai Chi may also be effective activities.[27]

Management of any psychiatric co-morbidity combined with stress management, e.g. planning and coping strategies, are essential parts of fibromyalgia treatment.[27]

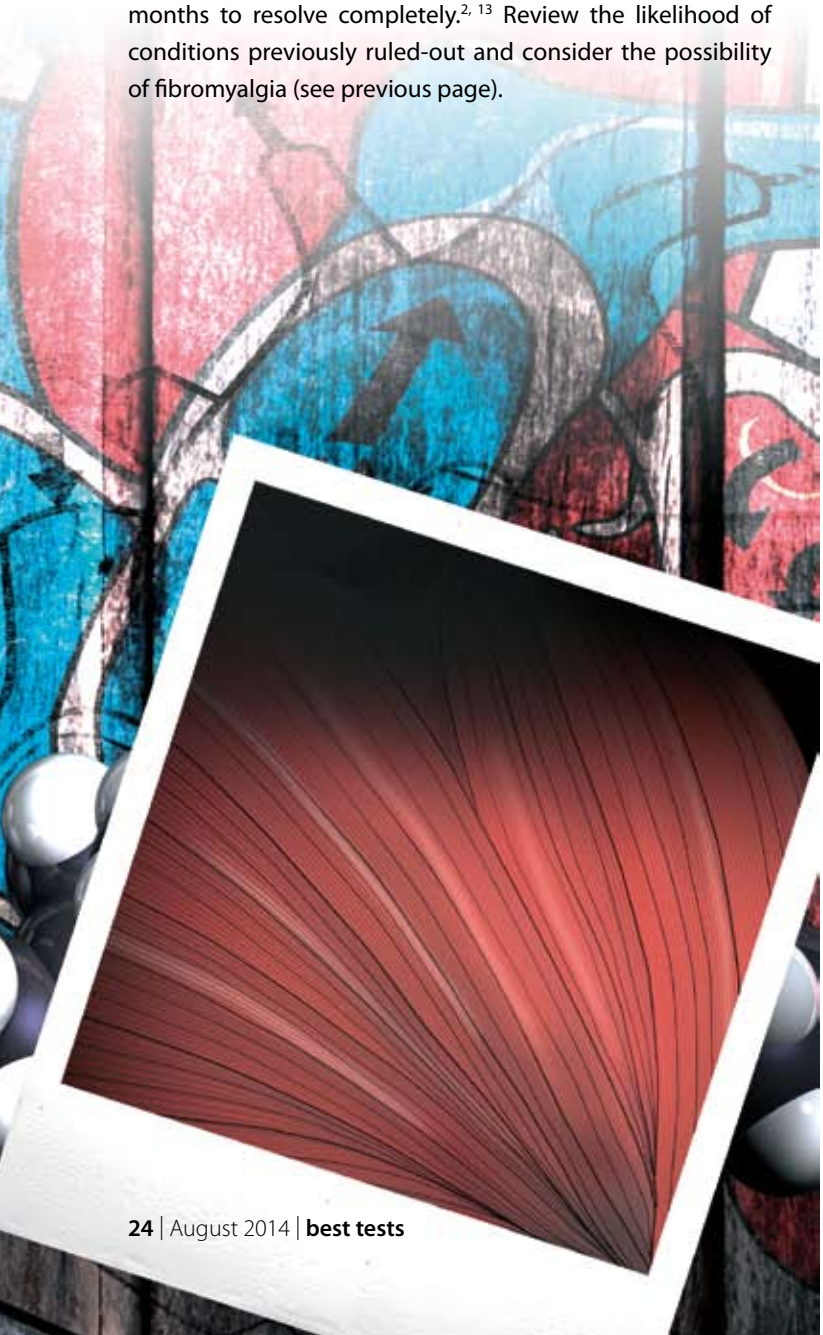
The pharmacological treatment of fibromyalgia is not routinely helpful; currently there are no medicines specifically indicated for the syndrome and patients with fibromyalgia can often experience adverse effects of medicines. Expert opinion is that paracetamol or NSAIDs may provide some relief.[27] Tricyclic antidepressants used off-label may also provide benefit,[27] and can improve sleep quality when taken at low doses. Amitriptyline is the tricyclic antidepressant with the best evidence base for fibromyalgia, e.g. amitriptyline, 10 –30 mg, an hour or two before going to bed.[27] Nortriptyline is also often used. The use of opioids in patients with fibromyalgia is not recommended.[27] Tramadol, however, is reported to provide benefit to some patients with fibromyalgia, via atypical pathways (as opposed to a class effect).[27]

The importance of diet, exercise and avoidance of smoking should be reiterated before considering offering patients alternative lipid-lowering medicines.[2] Expert opinion is that high-risk patients who are intolerant to statin treatment, may benefit from non-statin lipid-lowering medicines, e.g. gemfibrozil or nicotinic acid (see New Zealand Formulary for dosing details).[2] High-risk patients include those with any of the following:[2]

- Atherosclerotic cardiovascular disease
- Diabetes and age 40 – 75 years
- LDL-C ≥ 5.0 mmol/L and an elevated cardiovascular risk

Investigating patients with unresolved symptoms or persistently elevated creatine kinase

If the patient's symptoms or creatine kinase results have not resolved two months after the withdrawal of statin treatment then an alternative diagnosis should be reconsidered, although statin-associated symptoms may take up to three months to resolve completely.[2, 13] Review the likelihood of conditions previously ruled-out and consider the possibility of fibromyalgia (see previous page).



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