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CONTENTS

ARTICLE

Diagnosis and management of acute coronary syndromes

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acute coronary syndromes, antiplatelet drugs, antithrombotic therapy, myocardial infarction, troponin, unstable angina

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SUMMARY

Acute coronary syndromes are a significant cause of morbidity and mortality in Australia. Outcomes are likely to be improved by rapid and accurate diagnosis, and early intervention.

The development of high-sensitivity troponin assays has revealed previously unrecognised types of myocardial injury, for which conventional management guidelines for myocardial infarction may not confer similar benefits. The distinction between myocardial injury and myocardial infarction has therefore become increasingly important.

Once the diagnosis of acute myocardial infarction has been made, individualised acute reperfusion strategies including percutaneous coronary intervention or fibrinolytic therapy should be considered. Secondary prevention strategies should be implemented before hospital discharge.

Introduction

Acute coronary syndromes encompass myocardial infarction and unstable angina. Although survival has improved, acute coronary syndrome remains a significant cause of morbidity and mortality in Australia.

Previous management guidelines largely focused on timely coronary reperfusion to reduce the size of the infarcted area. Current management guidelines focus on the need to establish an accurate diagnosis of acute coronary syndrome. High-sensitivity troponin assays have led to greater and earlier identification of patients experiencing an acute coronary syndrome. However, the lowered troponin reference threshold has also unmasked a host of previously unrecognised types of myocardial injury for which conventional management may not confer similar survival benefits.

Differentiating myocardial infarction from myocardial injury

A diagnosis of myocardial infarction can no longer be based solely on elevated concentrations of troponin. Myocardial infarction as a result of atherosclerotic plaque rupture is termed a type 1 myocardial infarction in the Fourth Universal Definition of Myocardial Infarction (see Fig.).[1] The diagnosis requires elevated troponins in conjunction with a clinical history consistent with myocardial ischaemia, ischaemic changes on the ECG, or ancillary evidence of coronary ischaemia on cardiac imaging if available.[1]

Myocardial injury is defined as a troponin value at or above the 99th percentile upper reference limit derived from a normal reference population.[1] This may be acute or chronic.

It is important to differentiate that an acute myocardial injury may also be termed a type 2 myocardial infarction. In type 2 myocardial infarction, acute atherosclerotic plaque rupture is not a feature.[1] The acute myocardial injury arises due to a mismatch between oxygen supply and demand, when there is an acute stressor such as intercurrent illness, acute anaemia or sustained tachyarrhythmia, in patients with known or presumed coronary artery disease. The extent of the injury depends on pre-existing coronary artery disease, non-cardiac comorbidities and the severity of the acute stress.

A chronic elevation of troponin concentrations is more commonly seen in older patients with multiple comorbidities who have non-coronary conditions that result in chronically increased myocardial demands. Examples are chronic renal impairment and chronic heart failure.

Acute management

All acute care facilities with the capacity to treat myocardial infarction should have systematic processes and infrastructure to expedite urgent consultation with a cardiologist, including telephone consultation.

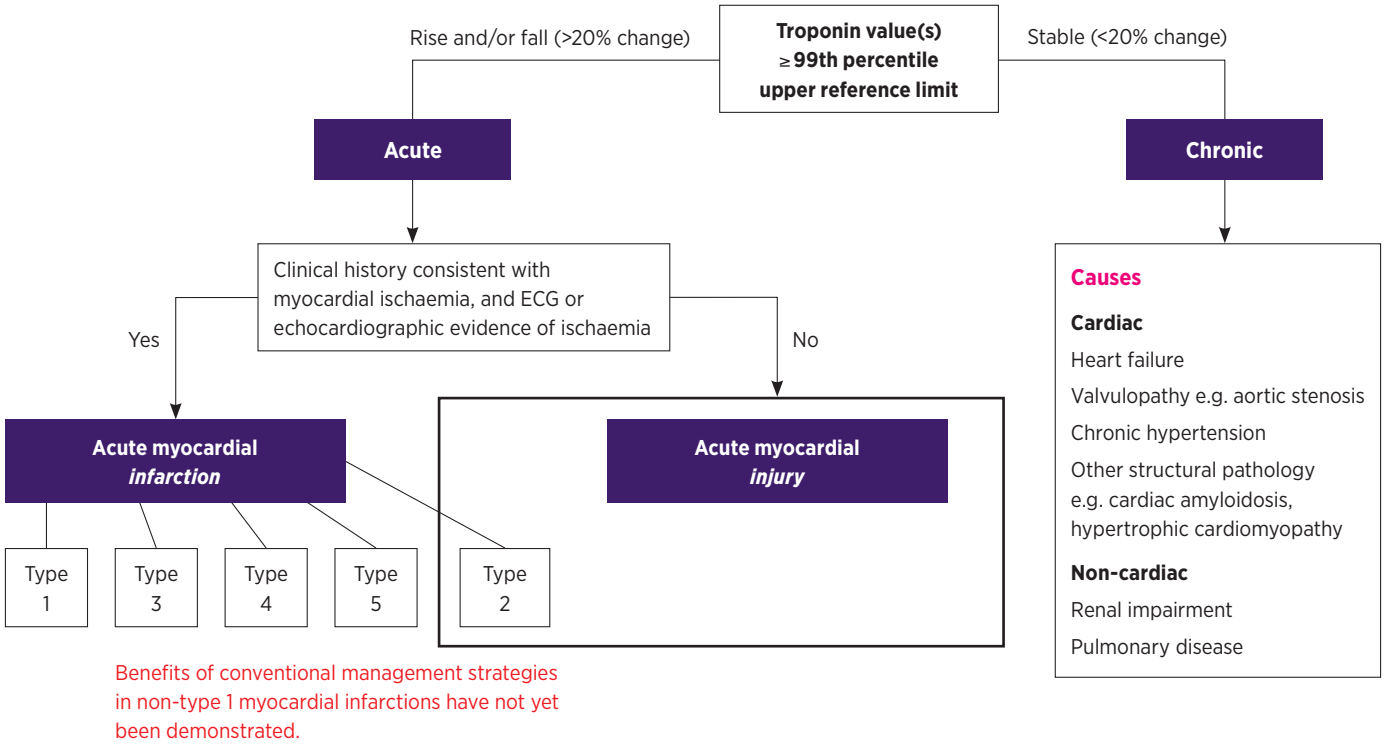
It is crucial to determine if there is ST-elevation on the ECG and to identify acute arrhythmic and haemodynamic complications. Acute management of such complications should be guided by the Australian Resuscitation Council Guidelines for Advanced Life Support,[2] in addition to support from intensive care or emergency medical retrieval services.

Initial management

Aspirin and other drugs are used in the early management of acute coronary syndrome.

This article is peer-reviewed

Fig. **Fourth universal definition of myocardial infarction**



Types of acute myocardial infarction

Type 1 = plaque rupture
Spontaneous myocardial infarction secondary to atherosclerotic plaque rupture

Type 2 = ischaemic imbalance
Tachyarrhythmia, anaemia, respiratory failure, hypotension/shock, severe hypertension, coronary vasospasm, acute myocarditis

Type 3 = biomarker values unavailable
Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes/left bundle branch block, however death occurred before initial or serial blood samples could be obtained

Type 4 = percutaneous coronary intervention-related
4a – secondary to procedure e.g. coronary dissection, no re-flow, distal embolisation
4b – associated with stent or scaffold thrombosis
4c – in-stent restenosis following balloon angioplasty in infarct territory when no other culprit lesion can be identified

Type 5 = coronary artery bypass grafting-related
Direct traumatic injury to myocardium

Adapted from reference 1

Nitrates

Glyceryl trinitrate is a potent vasodilator used to increase coronary blood flow. It is given sublingually or via intravenous infusion to provide symptom relief. Due to the potential adverse effect of hypotension, it should not be used if patients are hypotensive, or taking a phosphodiesterase-5 inhibitor.

Opioids

Morphine and fentanyl are potent analgesics. They are recommended for the relief of ischaemic chest pain.

Oxygen

The routine use of oxygen supplementation is not recommended in patients who are not hypoxic.

ST-elevation myocardial infarction

Patients with an ST-elevation myocardial infarction (STEMI) require interventions to re-establish coronary blood flow and minimise morbidity and mortality. This can be achieved by percutaneous coronary intervention or fibrinolytic therapy. Patient choice, ischaemic and bleeding risks must be carefully considered,[3] especially in patients with significant comorbidity or a short life expectancy.

In the absence of life-limiting comorbidities and contraindications, patients presenting within 12 hours of the onset of chest pain require emergency reperfusion. Primary percutaneous intervention is preferred if it can feasibly be performed within

90 minutes of first medical contact.[4] For Australians unable to reach a capable facility within this time, fibrinolytic therapy remains a life-saving option and should be administered promptly.[5] Early transfer for primary percutaneous intervention within 24 hours is reasonable,[6] however immediate transfer for rescue primary percutaneous intervention is critical if fibrinolytic therapy fails. This is evidenced by a reduction of 50% or less in ST-elevation on an ECG 60–90 minutes post-fibrinolysis, haemodynamic instability or persistent chest pain.[7]

Non-ST-elevation myocardial infarction

Compared to STEMI, the diagnosis of a non-STEMI is more complex to establish, due to the rising incidence of non-type 1 myocardial infarctions and myocardial injuries. Interpretation of the complete clinical presentation in the context of the Fourth Universal Definition of Myocardial Infarction is recommended rather than relying on troponin elevation alone. After a diagnosis of non-STEMI has been confirmed, acute management includes antiplatelet therapy and anticoagulation, and coronary investigation should be considered. This is because rates of recurrent myocardial infarction, refractory angina and rehospitalisation for recurrent acute coronary syndrome can be significantly decreased with percutaneous revascularisation.[8-12] In the absence of life-limiting comorbidities and contraindications, further investigation with primary percutaneous intervention should be considered especially if the patient has risk factors including diabetes, renal failure and heart failure.

Drug therapy

In addition to reperfusion, drug therapy improves the outcomes of acute coronary syndrome.

Antiplatelet drugs

Antiplatelet therapy is a cornerstone of acute coronary syndrome management.

Aspirin

Oral aspirin significantly reduces the risk of recurrent myocardial infarction, strokes and death at 12 months post-myocardial infarction.[13] In the absence of contraindications, a loading dose of 300 mg should be given as soon as possible after the patient presents. Maximum platelet inhibition occurs within two hours.

$P2Y_{12}$ inhibitors

$P2Y_{12}$ inhibitors available in Australia are clopidogrel and ticagrelor. The choice of drug varies between regions, however clinical guidelines recommend ticagrelor over clopidogrel in the absence of other considerations such as a need for long-term oral anticoagulation, an elevated bleeding risk or concerns about patient adherence with ticagrelor's twice-daily dosing regimen. This recommendation is due to a greater reduction in the 12-month composite end point of death from cardiovascular causes, stroke and myocardial infarction with ticagrelor compared to clopidogrel.[14] Patients should be given loading doses of ticagrelor (180 mg) or clopidogrel (600 mg or 300 mg) at the time of diagnosis. Peak platelet inhibition occurs within two hours with ticagrelor, two hours with clopidogrel 600 mg and eight hours with clopidogrel 300 mg.[15]

Pre-treatment with $P2Y_{12}$ inhibitors before coronary angiography is not necessary, in the absence of very high-risk features including ongoing chest pain or anticipated delays in angiography or the transfer to a primary percutaneous intervention centre, as pre-treatment does not reduce ischaemic events. Furthermore, the likelihood of requiring coronary artery bypass grafting surgery should be considered before administering $P2Y_{12}$ inhibitors. Patients with haemodynamic instability or extensive ischaemic ECG changes are more likely to require surgery, and $P2Y_{12}$ inhibitor therapy can delay surgery and increase perioperative bleeding.

Anticoagulation

The goal of anticoagulation in acute coronary syndrome is to prevent clot propagation or reformation, in combination with antiplatelet therapy. Enoxaparin or unfractionated heparin may be used.

In the case of fibrinolysis for patients with a STEMI, an intravenous bolus of enoxaparin 0.3 mg/kg is recommended for patients under 75 years old (not recommended above 75 years). This is followed by subcutaneous enoxaparin 1 mg/kg (up to a maximum dose 100 mg in people with normal renal function) and 0.75 mg/kg above the age of 75 years.

Anticoagulation should continue until a primary percutaneous intervention is performed. If a conservative, non-invasive strategy is adopted, anticoagulation should be given for at least 48 hours, or for the duration of hospitalisation up to eight days.[16-18] The patient's renal function should be checked before determining the ongoing anticoagulant dose.

Secondary prevention

Following acute management of myocardial infarction, secondary prevention strategies should start before the patient leaves hospital (see Table).[19] These strategies are vital in minimising the risk of further atherosclerotic cardiovascular events. Additionally, referral for cardiac rehabilitation is recommended for patients recovering from acute coronary syndrome.

Table **Drugs used in secondary prevention of acute coronary syndrome**

Drug	Recommendations
Aspirin	Continue indefinitely unless contraindicated.
$P2Y_{12}$ inhibitors	Continue for at least 12 months post-acute coronary syndrome, irrespective of whether coronary revascularisation has occurred, due to reduction in risk of recurrent acute coronary syndrome, stroke or death. Continuation beyond 12 months should be decided in conjunction with the treating cardiologist.
Statins	The highest tolerated dose of statins should be continued indefinitely to achieve low-density lipoprotein targets ≤1.8 mmol/L. Consider addition of ezetimibe. Consider PCSK9 inhibitor therapy if low-density lipoprotein remains >2.6 mmol/L despite maximally tolerated doses of statin and ezetimibe.
Renin–angiotensin antagonists	Post-acute coronary syndrome, ACE inhibitor or angiotensin receptor antagonist limit infarct size and left ventricular remodelling, and reduce overall cardiovascular mortality, non-fatal myocardial infarction and stroke.[3] These drugs should be increased to the highest tolerated doses for maximum benefit, especially if there is concurrent hypertension or left ventricular dysfunction.[19] Blood pressure targets of 130–140 mmHg systolic and 80–90 mmHg diastolic should be considered.
Beta blockers	The benefit of beta blockers is equivocal in patients with preserved left ventricular function, especially beyond one year after infarction, in the modern era of primary percutaneous coronary intervention. They can be used, however, if further antihypertensive drugs are required.

Conclusion

The guidelines for the management of acute coronary syndromes have evolved beyond providing a static framework to ensure timely coronary intervention to decrease morbidity and mortality. They now compel greater clinical judgement in redefining myocardial injury and myocardial infarction. This includes consideration of the patient's bleeding and ischaemic risk profile before intervention. The aim is to ensure delivery of appropriate care for the patients most likely to derive therapeutic benefits. <

Conflicts of interest: Derek Chew's institution has received research funds from AstraZeneca.

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Letters to the Editor

Multivitamin products may contain more than vitamins

Aust Prescr 2021;44:185
https://doi.org/10.18773/austprescr.2021.054

There are additional considerations regarding the safety of commonly used vitamins and minerals.[1] These include the addition of listed medicines to the Australian Register of Therapeutic Goods that style themselves as a multivitamin product but contain other ingredients. These may include chemicals (e.g. chromium picolinate, selenomethionine), other substances (e.g. concentrated fish omega-3 triglycerides) or various herbal substances (e.g. *Panax ginseng*, *Ginkgo biloba*). The consumer may not be alerted to the presence of these ingredients by the product name.

Changes to the *Therapeutic Goods Act 1989* following the recommendations of a review[2] have resulted in a cookbook list of 'permissible ingredients' in listed medicines. The Act requires that if the sponsor submits certain designated certifications, including that the product is safe for the purposes for which it is to be used, the relevant official in the Therapeutic Goods Administration (TGA) must list the medicine. The product may then be marketed in Australia.

It is only sometimes later, if at all, that the TGA will review those certifications, the product's presentation (including name) and evidence supporting the inclusion of other substances in a multivitamin product. There is no requirement that the evidence includes an adequate study of clinical efficacy and safety of the exact formulation used in the product. Australian consumers are being exposed to 'multivitamin' products with curious formulations and inadequate product names.

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Geraldine Moses AM, author of the article, comments:

It is a very valid point that many 'vitamin and mineral' products sold in Australia contain ingredients that are neither vitamins nor minerals. Given that the product names invariably give no hint that substances such as fish oil and *Ginkgo biloba* are co-formulated, it is possible that consumers are taking them unknowingly. The potential for adverse effects and drug interactions from these additional substances is likely be underestimated.

Although a comprehensive list of all ingredients is usually included on the labelling of medicines listed by the TGA, consumers may still be unaware that these substances are not vitamins or minerals. It would be preferable if the TGA required that multivitamin and mineral products stated clearly, in the brand name area of the labelling, that the product contains such substances in addition to the vitamins and minerals.

The Editorial Executive Committee welcomes letters, which should be less than 250 words. Before a decision to publish is made, letters which refer to a published article may be sent to the author for a response. Any letter may be sent to an expert for comment. When letters are published, they are usually accompanied in the same issue by any responses or comments. The Committee screens out discourteous, inaccurate or libellous statements. The letters are sub-edited before publication. Authors are required to declare any conflicts of interest. The Committee's decision on publication is final.

LETTERS

Midodrine efficacy

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I would like to raise attention to the inaccurate representation of midodrine efficacy in the new drug comment on midodrine for orthostatic hypotension.[1]

The pivotal study in the regulatory submission reported that the three-times-a-day regimen demonstrated a clinically and statistically significant benefit to patients in the treatment group and that the benefits of midodrine were sustained throughout the treatment period.[2] Further, the efficacy and safety of midodrine was supported by 11 clinical studies and two meta-analyses from which the Therapeutic Goods Administration (TGA) concluded evidence exists in support of the cardiovascular benefit and symptomatic improvement in the target population.

The new drug comment leads physicians to believe the efficacy and clinical benefit of midodrine has not been established. It is essential physicians are exposed to information that accurately reflects the totality of the evidence supporting the clinical efficacy of midodrine while making their decision to prescribe to the target demographic who would most benefit. That midodrine was once supplied under the Special Access Scheme is demonstrable of the medicine meeting an important unmet need in the Australian community.

Midodrine was approved by the US Food and Drug Administration (FDA) in September 2010 following the receipt of postmarketing confirmatory trial results demonstrating the medicine's clinical benefit. It is also noted the decision to reverse the FDA's proposal to withdraw midodrine was at the appeal of professional organisations, healthcare professionals, and indeed patients.

The clinical benefits of midodrine in the management of orthostatic hypertension symptoms are acknowledged globally, the medicine being approved in the USA, European Union and New Zealand.

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The Editor John Dowden comments:

The new drug comment on midodrine prepared by the Editorial Executive Committee took into consideration the clinical evaluation report prepared for the Therapeutic Goods Administration. That report is reflected in the published Australian Public Assessment Report (AusPAR).[1]

While the AusPAR reports a haemodynamic benefit and symptom improvement with midodrine, it also comments that the clinical dossier does not provide compelling evidence of efficacy.[1] Readers are encouraged to look at the evidence in the AusPAR and draw their own conclusions about the clinical effectiveness of the drug.

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ARTICLE

Medical abortion in primary care

SUMMARY

Early medical abortion is a safe, cost effective and acceptable alternative to surgical abortion. It offers privacy and autonomy and can be provided by general practitioners who have completed an online training module.

Abortion can be induced with mifepristone and misoprostol up to nine weeks of gestation. Apart from anticoagulation and severe anaemia, there are few contraindications and precautions for medical abortion.

Obtaining informed consent requires the provision of information on expected effects, adverse effects and complications. The woman must know when to present to an emergency department.

Follow-up must be arranged to ensure the abortion is complete. A serum human chorionic gonadotropin concentration or a low-sensitivity urine pregnancy test is used to confirm completion.

Most contraceptive methods can be started immediately following medical abortion. If an intrauterine device is preferred, it should be inserted after confirming the abortion is complete.

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induced abortion, mifepristone, misoprostol

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Introduction

In Australia, approximately 25% of pregnancies are unplanned, of which one-third end in abortion. Early medical abortion is an alternative to surgical abortion for pregnancies up to nine weeks gestation. It is generally less costly than surgical abortion and the drugs used (mifepristone and misoprostol) are subsidised by the Pharmaceutical Benefits Scheme. Early medical abortion offers privacy and autonomy. It can be supported by telemedicine and generally avoids the need for invasive surgical procedures.[1] Clinical advice in this article is based on the medical abortion section of Therapeutic Guidelines: Sexual and Reproductive Health.[2]

Medical abortion in primary care

Currently only around 2850 of the 41,000 GPs in Australia are registered to prescribe the mifepristone and misoprostol regimen for medical abortion. To register they must complete the free 3–4 hours online training of the MS-2 Step Prescribing Program. This is mandatory except for those who hold a current Fellowship or Advanced Diploma of the Royal Australian and New Zealand College of Obstetricians and Gynaecologists.

While women need advice about what early medical abortion involves, the majority do not require counselling about their decision to have an abortion, although some will require additional support. A Medicare rebate is available for up to three non-directive counselling sessions on pregnancy options delivered by an endorsed GP, psychologist, social worker or mental health nurse. For women without contraindications to either medical or surgical abortion the relative advantages and disadvantages of both methods should be discussed (Box 1). When feasible, the chosen method should be offered or facilitated.

Contraceptive options are important to raise before an abortion. This includes discussing long-acting reversible contraceptive methods. Support for clinicians providing, or considering providing, medical abortion in primary care is available through the Australian Contraception and Abortion Primary Care Practitioner Support Network (AusCAPPS).

Contraindications

There are few contraindications to medical abortion for women with a confirmed intrauterine pregnancy of no more than 63 days. Important contraindications are shown in Box 2. Breastfeeding and multi-fetal pregnancies are not contraindications. Early medical abortion is clinically preferred over surgical abortion if there are anaesthetic risks and may be safer for obese women and those with distortion of the uterine cavity due, for example, to large fibroids.

Precautions

Specialist advice is required for women with severe anaemia, ischaemic heart disease and severe renal or respiratory disease. Due to the antiglucocorticoid effects of mifepristone, specialist advice is needed for those with asthma that is difficult to control. This is because there may be no effect if the patient needs

to increase the dose of the corticosteroid she uses for asthma control. For those with stable asthma on long-term inhaled preventer therapy, review the asthma plan to ensure appropriate steps can be taken in case of an exacerbation. Careful glucose monitoring may be needed for women using insulin because of possible vomiting, altered food and liquid intake, and potential dehydration during the abortion. Additional care is also required for women with epilepsy who have seizures induced by vomiting or pain.

Box 1 Relative advantages of medical and surgical abortion[2]

Medical abortion

Usually avoids invasive procedures and potential surgical complications (e.g. uterine perforation, anaesthetic risk)*

May be safer for individuals with obesity or distortion of the uterine cavity

May be more widely accessible

Usually less costly

Usually allows abortion to take place at home

Seen by some individuals as a more natural and less medical process

Surgical abortion

Less likely to require subsequent evacuation of retained products*

Requires only one appointment and is usually performed under sedation

Causes less pain

Bleeding resolves in a few days rather than weeks

Less risk of severe bleeding and access to emergency care not usually required

Avoids potential distress of seeing the gestational sac

* In 3–5% of medical abortions and less than 1% of surgical abortions, subsequent surgical evacuation of retained products of conception is required.

Box 2 Contraindications and precautions in medical abortion

Contraindication to mifepristone and misoprostol combination

Intrauterine device (IUD) in place – if the IUD cannot be removed, a surgical abortion is the recommended safe option

Haemorrhagic disorder or treatment with anticoagulants

Long-term use of an oral corticosteroid (effectiveness may be reduced by the antiglucocorticoid action of mifepristone)

A travel time to hospital emergency services with blood transfusion services of more than two hours in the 14 days after taking mifepristone

Confirmed or suspected ectopic pregnancy

Hypersensitivity to mifepristone, misoprostol (or any prostaglandin)

Uncertainty about gestational age

Inherited porphyria – there is a theoretical risk of precipitating or exacerbating attacks of porphyria, but no data are available

Precautions for mifepristone and misoprostol combination

Severe anaemia

Ischaemic heart disease

Asthma that is unstable or treated with long-term preventer therapy

Insulin requiring diabetes

Epilepsy

Investigations

Before a medical abortion it is important to confirm that there is an intrauterine pregnancy. The mifepristone and misoprostol combination is not effective for ectopic pregnancy.*

Ultrasound

An intrauterine pregnancy is confirmed by the presence of either a fetal pole or yolk sac. These structures are usually visible at 5–6 weeks gestation on a high-quality vaginal ultrasound. Confirmation may be delayed if transabdominal ultrasound is used, particularly in obese women.[2]

Human chorionic gonadotropin

Measurement of the quantitative serum human chorionic gonadotropin (HCG) concentration is recommended on the day (or as soon as possible before) mifepristone is taken. This baseline value enables comparison with a repeat measurement seven days after the dose of mifepristone, to confirm completion of the abortion.

For pregnancies that are suspected to be less than six weeks, the serum HCG can be useful to guide the timing of the ultrasound. This reduces the need for a repeat scan.

If the HCG is more than 5400 IU/L, there is a 90% chance a fetal pole or yolk sac will be detected on a high-quality vaginal ultrasound. At lower concentrations ultrasound can be delayed, unless there is suspicion of ectopic pregnancy.

Other investigations

Investigations to be considered include:

- screening for sexually transmitted infections (chlamydia, gonorrhoea)
- haemoglobin and iron studies if anaemia is known or suspected, for example in women with heavy menstruation or from populations with a high prevalence of iron deficiency.

Procedure

The woman must give informed consent for the procedure. This includes provision of information about how to take the drugs, their expected effects, adverse effects and possible complications, including advice on when to present to an emergency department.

* A clinical trial is currently underway in Australia of very early medical abortion (VEMA) before an intrauterine pregnancy can be confirmed. VEMA is not yet mainstream practice.

The regimen for medical abortion is supplied in a composite pack containing one mifepristone 200 mg tablet and four misoprostol 200 microgram tablets. Mifepristone blocks the action of progesterone which supports the endometrium in a continuing pregnancy. It also softens and dilates the cervix, increases uterine activity and increases sensitivity to misoprostol. Misoprostol is a synthetic prostaglandin E_1 analogue which softens the cervix and induces uterine contractions to expel the pregnancy.

Step 1: Mifepristone is taken orally. Adverse effects are uncommon, but if vomiting occurs within one hour of ingestion, the dose must be repeated. Normal activities can be continued. Light bleeding is common. The pregnancy is expelled in only around 5% of cases before taking misoprostol, however it is important the misoprostol is taken as planned to reduce the chances of retained products.

Step 2: It is recommended that pre-medication with an antiemetic and a non-steroidal anti-inflammatory drug is taken 30–60 minutes before misoprostol and that a small quantity of stronger analgesics is supplied for use if needed. Stronger analgesics may be taken before misoprostol to manage pain. Some women choose to use these only if necessary. Misoprostol is taken buccally 36–48 hours after mifepristone at a pre-arranged time to suit the patient's schedule. The mouth is rinsed with water and two tablets are placed on each side between the lower gums and cheeks and held in place for 30 minutes. Any residual material is then swallowed. Misoprostol can cause adverse effects including nausea, headaches, fever and diarrhoea.[3-5]

Expected effects

Cramping pain, generally worse than menstrual pain, can start within 1–4 hours of taking misoprostol. Bleeding generally follows pain and is usually heavier than normal menstruation and blood clots are usual. This bleeding generally settles after the products of conception are passed. The conceptus is more likely to be seen with later gestations. This is distressing for some women and reassuring for others.

Bleeding remains similar to menstruation for 5–7 days before gradually decreasing. Fluctuations in the amount of bleeding and clots are common. Bleeding stops by day 14 in approximately 65% of cases, but light bleeding or spotting can persist for 4–5 weeks.

Follow-up

All women should be followed up after early medical abortion. Printable information for patients is available from Therapeutic Guidelines: Sexual and Reproductive Health (Fig).[2] This includes advice on avoiding intercourse, tampons, baths and swimming for seven days to reduce the risk of infection. There is guidance on when to present to an emergency department in the event of heavy bleeding or severe pain.

Anti-D prophylaxis for Rhesus-negative patients is no longer required for early medical abortion up to 10 weeks gestation.[6]

Check-in call at three days

Most practitioners schedule a routine call with the patient around three days after mifepristone is taken to check whether the bleeding was as expected. This is also to check for possible complications associated with ongoing pain, heavier than expected bleeding or ongoing symptoms of pregnancy.

There are two methods to confirm there is no ongoing viable pregnancy. The most common method is to measure the serum HCG concentration. There should be an 80% or greater fall from the baseline test to a follow-up test seven days after taking mifepristone. Alternatively, a low-sensitivity urine pregnancy test can be supplied for home use 16–21 days after the mifepristone is taken. If the test is positive, the serum HCG must be measured to exclude ongoing pregnancy. Standard urine pregnancy tests are unsuitable. They are sensitive to 25 IU/L so are likely to remain positive for several weeks after a medical abortion. Low-sensitivity tests only detect HCG concentrations over 1000 IU/L. Routine use of ultrasound to assess the outcome is not recommended.

Follow-up at 2–3 weeks

The 2–3-week follow-up can be in person or by telehealth methods. The aim is to check that the abortion has been successful with no ongoing viable pregnancy, that there are no symptoms suggestive of complications and to ensure contraceptive needs are met.

A range of emotions may be experienced before and after an abortion including grief and sadness, but for most women these are transient and often accompanied by relief. Some people will experience distress and may require extra support and referral to a mental health practitioner. Additional care may be required for women with a pre-existing mental health disorder. There is no evidence that abortion is associated with an increased risk of adverse mental health outcomes compared to continuing with an unplanned pregnancy.[5,7]

Contraception after medical abortion

Another pregnancy is possible soon after an abortion. With the exception of an IUD, all contraceptive methods can be started soon after taking mifepristone (Table). There is a theoretical concern that progestogen-only methods, started before taking mifepristone, could

Fig. **Advice after a medical abortion**

Therapeutic Guidelines

Advice after a medical abortion

General advice after a medical abortion

A follow-up blood test is very important to check that the abortion has been successful. The test needs to be taken 7 days after you took the first tablet (mifepristone). Other forms of testing may be appropriate for some people, but your clinic will discuss these with you if they are an option.

For 7 days after taking the second tablet (misoprostol), to reduce the risk of infection, avoid:

- sexual intercourse
- use of tampons or menstrual cups
- swimming
- taking a bath or using a spa.

When to go to an emergency department

Go to an emergency department if **at any time** you have:

- very heavy bleeding, such as **any** of the following:
  - your bleeding fills more than two large pads in an hour for more than 2 hours in a row
  - you are passing clots the size of a small lemon or larger
  - you feel faint and think the bleeding is heavy even if you are not sure about how much you are bleeding
- any of the following symptoms (which could mean an ectopic pregnancy in the Fallopian tube):
  - severe abdominal (tummy) pain
  - pain in your pelvis on one side
  - pain in the tips of your shoulders
- other concerns and you don't have access to medical advice (eg from the prescribing clinic).

When to contact the clinic that prescribed the abortion drugs

If you have any of the symptoms below, you might still be pregnant. Contact the clinic if:

- **at 24 hours** after taking misoprostol, you either:
  - have had no or little bleeding (less than a normal period), or
  - have not passed any pregnancy tissue, or any clots larger than a small grape
- **at 48 hours** after taking misoprostol, you still have nausea
- you had some initial bleeding, but it stopped within **4 days** of taking misoprostol
- **at 14 days** after taking misoprostol, you still have breast tenderness.

If you have any of the symptoms below, there might still be some pregnancy tissue (eg placenta) in the uterus (womb). Contact the clinic if:

- **at 7 days** after taking misoprostol:
  - you are still passing clots
  - you still have cramping pain
  - you still have bleeding that is heavier than a period
  - you have bleeding that stopped and restarted and has been as heavy as a period for the last 24 hours or more
- **at 14 days** after taking misoprostol you have bleeding that is not much less than when it started
- **at 4 to 5 weeks** after taking misoprostol you still have bleeding that is different to your usual menstrual cycle.

Contact the clinic if you have any of the symptoms below, as they can indicate that you have an infection of the uterus:

- pelvic pain
- pain during sex
- unusual vaginal discharge
- fever (over 38°C)
- tenderness on touching the abdomen (tummy) or pelvis
- nausea or vomiting
- feel unwell.

Contact the clinic that prescribed the abortion drugs if you have any concerns about the medical abortion.

Doctor's contact details:

Therapeutic Guidelines Limited (www.tg.org.au) is an independent not-for-profit organisation dedicated to deriving guidelines for therapy from the latest world literature, interpreted and distilled by Australia's most eminent and respected experts.

reduce the effectiveness of mifepristone. While evidence is limited, those choosing a depot injection should be advised of this potential effect. A number of studies have shown the contraceptive implant does not affect the efficacy of mifepristone.[4]

Complications

Complications of early medical abortion are uncommon, but important to recognise and manage appropriately. The complication rates from international and national data are:

- retained products of conception requiring surgical intervention – up to 5%
- continuing viable pregnancy – 0.8%
- upper genital tract infection requiring intravenous antibiotics – 0.1–0.2%
- haemorrhage requiring transfusion – 0.1%.[8]

The advice given to women on the symptoms that warrant going to an emergency department can be supported by the printable patient information sheet from Therapeutic Guidelines (Fig.).

Retained products of conception

The retention of tissue after passage of the conceptus is suspected by ongoing heavier than expected bleeding and cramping. Retained products can be confirmed by ultrasound, but this is not always necessary if the person is well and the bleeding is settling.

Management depends on symptoms such as painful cramping, the size of the retained products, the development of anaemia and the patient's preferences. The options are expectant management, or repeat dosing of misoprostol (400 microgram buccally, with an additional 400 microgram buccally in four hours if no significant bleeding has occurred), or surgical curettage. Antibiotics are required if infection is suspected.

Continuing pregnancy

An ongoing viable pregnancy should be suspected if little, light or no bleeding occurred within 24 hours of taking misoprostol, particularly if products of conception were neither seen nor felt to have passed and pregnancy symptoms are continuing. An ultrasound and quantitative HCG are generally required. If pregnancy is confirmed and the gestation remains within 63 days, mifepristone and misoprostol can be repeated, otherwise a surgical procedure is required. If the woman wants to continue with the pregnancy, she must be informed that there may be a risk of significant fetal abnormality. Referral for specialist management of the pregnancy is recommended.

Table **Medical abortion and starting contraception**

Contraceptive method	Timing of initiation	Time to effectiveness
Etonogestrel implant Medroxyprogesterone acetate injection	On the day of or within 5 days of taking mifepristone	Immediately
	More than 5 days post mifepristone*	7 days
Intrauterine devices	Exclude new pregnancy Insert after completion of abortion, provided no symptoms of retained products, or at the time of the first menstrual period Encourage hormonal bridging method until insertion	Copper IUD: immediately Hormonal IUD: 7 days or immediately if day 1–5 of menstrual cycle
Combined hormonal contraception † and progestogen-only pill	Within 5 days of taking mifepristone	Immediately
	More than 5 days post mifepristone*	7 days ‡

IUD intrauterine device

* Exclude new pregnancy. A follow-up pregnancy test is required if pregnancy is not excluded

† Vaginal ring inserted after the heaviest bleeding has decreased

‡ Three consecutive pills (over 48 hours) for norethisterone 350 microgram and levonorgestrel progestogen-only pill.

Upper genital tract infection

Infection can present with subtle symptoms. Most cases are associated with retained products of conception. Upper genital tract infections are polymicrobial, most commonly involving anaerobic vaginal bacteria. Severe infections can be caused by *Clostridium* species or *Streptococcus pyogenes*. Sexually transmitted infections *Chlamydia trachomatis*, *Neisseria gonorrhoea* and *Mycoplasma genitalium* must also be considered.

Treat suspected endometritis with oral amoxicillin in combination with clavulanic acid for seven days (private script or streamlined authority is required for courses longer than five days). Severe infection will require inpatient intravenous antibiotics. Consider sexually transmissible infections in at-risk unscreened patients.

Conclusion

Early medical abortion in primary care offers an alternative safe and effective choice to surgical abortion. General practitioners are ideally placed to support their patients' reproductive health and autonomy by providing medical abortion and follow-up care. <

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ARTICLE

Non-anaemic iron deficiency

SUMMARY

Iron deficiency without anaemia is common. Patients may present with unexplained, non-specific symptoms.

Iron studies will usually show a low ferritin and low transferrin saturation with a normal haemoglobin concentration. The cause of the iron deficiency should be identified and managed.

There is limited evidence about the benefits of giving iron to people who do not have anaemia. If there is iron deficiency, most people can be given oral iron supplements.

Iron studies are repeated after 60–90 days of oral iron supplements. Further investigations are needed if the iron deficiency has not been corrected.

Some patients, including those who have not responsed to oral supplements may benefit from intravenous iron. There is no role for intramuscular injections of iron.

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dietary iron, ferritin, iron deficiency, iron supplements, transferrin

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Introduction

Iron deficiency is the most common mineral deficiency and iron deficiency anaemia affects approximately 20% of the world's population. Iron deficiency without anaemia is even more common.[1] It is an important public health problem in Australia. The World Health Organization (WHO) estimates that 8% of preschool children, 12% of pregnant women and 15% of non-pregnant women of reproductive age in Australia have anaemia, with iron deficiency being the major cause.[2] Anaemia is highly prevalent in indigenous communities. A study of an Aboriginal community in Western Australia identified anaemia among 55% of women and 18% of men.[3] Although it is three times as common as iron deficiency anaemia, iron deficiency without anaemia is an under-recognised and undertreated condition.[4]

Iron deficiency

Approximately 70% of the iron in adults is found within haemoglobin in red blood cells so anaemia is the most readily recognised effect of iron deficiency. However, it is now apparent that iron deficiency in the absence of anaemia also has unfavourable consequences.

While there is extensive literature surrounding iron deficiency anaemia, there is a paucity of evidence in non-anaemic iron deficiency. The current literature is predominantly based on small studies with often heterogeneous populations. As a result, there are no firm pathways to guide investigations, treatment and monitoring.

Presenting problems

Iron is an essential element, required for several metabolic pathways and responsible for the delivery of oxygen to organs and body tissues. A deficiency can therefore result in a wide range of symptoms that are non-specific and may not be initially recognised as being due to iron deficiency.

Iron deficiency without anaemia has been associated with:

- weakness, fatigue, reduced exercise performance, difficulty in concentrating, and poor work productivity[5]
- neurocognitive dysfunction including irritability[6]
- fibromyalgia syndrome[7]
- restless legs syndrome[8]
- symptom persistence in patients treated for hypothyroidism[9]
- poor neurodevelopmental outcomes in infants born to mothers with iron deficiency.[10]

Diagnosing iron deficiency

Iron deficiency can occur secondary to inadequate dietary intake, increased requirements (e.g. pregnancy and breastfeeding), impaired absorption (e.g. coeliac disease, bariatric surgery), or blood loss (e.g. menstrual, blood donation, gastrointestinal). A drug history should be taken particularly regarding anticoagulants, over-the-counter non-steroidal anti-inflammatory drugs and antiplatelet drugs. The underlying cause of iron deficiency should always be sought and managed.

Table 1 **Iron studies in the differential diagnosis of iron deficiency**

Test	Iron deficiency without anaemia	Iron deficiency anaemia	Anaemia of chronic disease	Iron deficiency anaemia and anaemia of chronic disease
Haemoglobin	N	↓	↓	↓
Mean cell volume	N or ↓	↓	N (or mildly ↓)	↓
Serum ferritin	↓	↓	N or ↑	↓ or N
Total iron-binding capacity	N or ↑	↑	↓ or N	N or ↑
Transferrin saturation	↓ or N	↓	↓ or N	↓
Soluble transferrin receptor	N or ↑	↑	N	↑

N = normal, ↓ = decreased, ↑ = increased

Iron studies assist in the differential diagnosis of iron deficiency (Table 1). A reduced ferritin is the most reliable initial marker to diagnose iron deficiency without anaemia. Although WHO defines low serum ferritin as less than 12 microgram/L in adults, a concentration of less than 30 microgram/L has a high sensitivity (92%) and specificity (98%) for iron deficiency,[11] correlating with the absence of iron stores in the bone marrow (see Table 2). Changes in iron status before the development of anaemia may be suggested on a full blood count by falling values for mean cell haemoglobin and mean corpuscular volume and an increased red cell distribution width.

Ferritin is an acute-phase protein so it rises in inflammatory conditions and in the elderly. This can make the diagnosis of iron deficiency challenging. In these cases, a higher ferritin threshold (<100 microgram/L) with a low transferrin saturation (<20%) can be used. To diagnose iron deficiency in patients with heart failure, the European Society of Cardiology has recommended a ferritin concentration below 100 microgram/L, or below 300 microgram/L with a transferrin saturation below 20%.[12] In chronic kidney disease, the Kidney Disease Improving Global Outcomes guideline advises iron supplements if ferritin is below 500 microgram/L and the transferrin saturation is less than 30%.[13]

An elevated plasma concentration of the soluble transferrin receptor is another useful biochemical marker for iron deficiency which can be used to distinguish it from anaemia of chronic disease. However, there is currently no Medicare rebate for this test. The gold standard for the diagnosis of iron deficiency is a bone marrow biopsy, but this is not commonly used.[14]

Table 2 **Ferritin and transferrin thresholds for the diagnosis of iron deficiency**

Patients and conditions	Ferritin concentration	Transferrin saturation
General population	<30 microgram/L	–
Inflammatory states	<100 microgram/L	<20%
Heart failure	<100 microgram/L	–
	<300 microgram/L	<20%
Kidney disease	<500 microgram/L	<30%

Correction of iron deficiency

The goal of treatment is to replenish iron stores and improve symptoms. Management initially should involve dietary counselling and oral supplements.

The evidence regarding the benefit of iron replacement in non-anaemic iron deficiency is based on several small trials and observational studies, mainly in women of reproductive age and patients with heart failure (Table 3).[5,10,12,15-19]

The treatment of non-anaemic iron deficiency is similar to the treatment of iron deficiency anaemia. The underlying aetiology must be identified and if possible corrected.

Optimising nutritional iron intake can be achieved by integrating dietary haem iron and free iron. Haem iron (liver, red meat, seafood, poultry) has a superior gastrointestinal uptake compared to free iron (plant-based). Vegetarians can maintain adequate iron intake if a wide variety of non-haem iron is consumed in foods such as wholegrains, legumes, nuts, seeds, dried fruits and green leafy vegetables, but these strategies are unlikely to be sufficient to correct

Table 3 **Benefit of correcting iron deficiency**[5,10,12,15-19]

Condition	Evidence
Fatigue and neurocognitive dysfunction	Improves fatigue in some studies but impact on neurocognitive dysfunction is uncertain[15]
Fibromyalgia	Improves symptoms of fibromyalgia, possibly related to the role of iron as a cofactor in neurotransmitter synthesis[16]
Restless legs	Small, randomised trials have shown improved symptoms with iron supplementation if the serum ferritin is ≤75 microgram/L[17]
Thyroid disease	Case reports describe correction of iron deficiency improving persistent symptoms in patients treated for hypothyroidism with adequate levothyroxine therapy[5]
Heart failure	Several randomised clinical trials in patients who have heart failure with reduced ejection fraction and iron deficiency have reported improvements in symptoms and quality of life after intravenous iron therapy[12]
Chronic kidney disease (haemodialysis)	Intravenous iron in patients with ferritin <700 microgram/L and transferrin saturation <40% results in less need for erythropoiesis-stimulating drugs, possible cardiovascular benefits and reduced blood transfusion requirements[18]
Inflammatory bowel disease	Correction of non-anaemic iron deficiency in patients with inflammatory bowel disease may improve quality of life[19]
Pregnancy	Iron deficiency should be corrected before and during pregnancy to prevent impaired neurocognitive function (poor memory and slower neural processing) in the child[10]

iron deficiency. Inhibitors of iron absorption (tea, coffee, cocoa, and red wines) should be avoided. This strategy is appropriate for asymptomatic patients who are not at risk of poor absorption.

Iron supplements

Oral iron therapy is the first-line and safest treatment for symptomatic patients or patients at risk of developing anaemia. It is convenient and cost effective. A number of different iron supplements are available in Australia, however, ferrous salts (fumarate, sulphate, gluconate) are preferred as they are the best absorbed. Guidelines recommend that patients should be counselled to take their iron supplements one hour before or two hours after food. Sometimes it may be possible to compromise on the timing of the dose if this helps the patient adhere to therapy. To improve tolerability, increase adherence to therapy and improve absorption, alternate-day dosing (60–200 mg, depending on tolerability) is superior to daily dosing.[20]

While there are several advantages of oral supplementation, gastrointestinal adverse effects such as nausea, epigastric pain and diarrhoea reduce adherence. Controlled-release preparations and iron polymaltose complex are reported to have a lower incidence of gastrointestinal adverse effects, however, the iron polymaltose complex is expensive which limits its use.[21,22]

Vitamin C co-administration has long been recommended to improve oral iron absorption. However, a recent study reported no significant between-group difference for the mean change in serum ferritin at eight weeks.[23]

If parenteral iron supplementation is required, intravenous iron is indicated. There is no role for intramuscular therapy. The intravenous preparations available are ferric carboxymaltose, ferric derisomaltose, iron polymaltose and iron sucrose. The use of intravenous iron should be limited because of its adverse effects, including permanent skin staining,[24] hypophosphataemia and rarely anaphylaxis.[25,26] Intravenous iron should be avoided if there is active systemic infection to avoid any possibility that iron may promote microbial growth and disrupt immune responses. The main indications for intravenous iron include:

- unsuccessful oral therapy – failure, poor adherence, intolerance
- malabsorption (e.g. coeliac disease, bariatric surgery)
- inflammatory bowel disease
- chronic kidney disease receiving erythropoiesis-stimulating drugs
- rapid increase in iron required (e.g. pre-operatively for urgent surgery or following acute blood loss)
- heart failure.

SELF-TEST QUESTIONS

True or false?

1. Iron deficiency requires further assessment to determine the cause even if there is no anaemia.
2. Giving oral iron on alternate days increases adherence to treatment.
3. When parenteral iron is indicated, intravenous iron is preferred over intramuscular iron.

Answers on page 209

Follow-up

After oral supplements have been taken for 60–90 days, fasting iron studies are repeated one week after stopping therapy to check if the iron deficiency has been corrected. Serum iron has a diurnal variation and the ideal specimen is a fasting morning sample after oral iron supplementation has been withheld for at least 24 hours before testing. If repletion has not occurred, re-investigation is recommended. Iron studies should be repeated approximately 60–90 days, or as clinically appropriate, after intravenous iron therapy.

If there is no response to oral iron therapy or if iron deficiency recurs, further investigations should be considered to exclude blood loss or malabsorption. A fall in haemoglobin concentration may be significant even if the patient does not become anaemic. Depending on the clinical findings, referral to a gynaecologist or a gastroenterologist may be appropriate.[27]

Conclusion

The correction of iron deficiency before the development of anaemia may improve symptoms and the patient's quality of life, but the supporting evidence is variable. Management of iron deficiency requires identification and investigation. For uncomplicated iron deficiency, oral iron is readily available, effective, safe, convenient and cost effective. For those patients intolerant of oral iron or with conditions where oral iron is likely to be ineffective or harmful, the intravenous route is preferred. ≺

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Testing for cirrhosis

SUMMARY

Cirrhosis can be suspected by a thorough clinical assessment, but compensated liver disease is often asymptomatic. Select investigations are therefore critical for identifying patients with advanced liver disease and cirrhosis.

Biomarkers and validated serum tests can evaluate liver damage and synthetic function. The ratio of the concentration of aspartate aminotransferase to the platelet count can predict the presence of cirrhosis.

Non-invasive imaging techniques, from basic ultrasound to elastography, are critical adjuncts to the clinical assessment of cirrhosis. They reduce the need for liver biopsy.

Careful monitoring, prescribing and appropriate specialist referral are key considerations in cirrhosis management. Early diagnosis can help to improve the outcomes for patients.

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cirrhosis, liver function, liver biopsy

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Introduction

Morbidity and mortality from liver cirrhosis are rising in Australia and worldwide. The diagnosis of cirrhosis is important to guide treatment, determine prognosis, and to monitor for complications in patients with chronic liver disease. The identification of cirrhosis is important for the prescribing of medicines, as its presence will alter the pharmacokinetics of some drugs.

Regardless of the cause of liver disease, cirrhosis results from liver injury that leads to inflammation and fibrogenesis. It causes distortion of hepatic architecture, with micro- and macroscopic nodularity, leading to portal hypertension.[1] Cirrhosis leaves patients vulnerable to life-threatening complications, including variceal bleeding, ascites, infection and hepatocellular carcinoma, and ultimately death.

Clinical features of cirrhosis

Most chronic liver disease is asymptomatic until decompensated cirrhosis develops. The diagnosis of early cirrhosis therefore requires a clinical suspicion of liver disease. Patients in Australia at risk of cirrhosis include those with a history of:

- chronic alcohol misuse
- obesity or other features of metabolic syndrome
- migration from countries with high endemic rates of chronic hepatitis B
- risk factors for chronic hepatitis C, such as a history of intravenous drug use
- haemochromatosis.

Clinical symptoms for those with early or compensated cirrhosis are often non-specific and include anorexia, weight loss and fatigue. Patients with decompensated cirrhosis may present with jaundice, confusion, abdominal distension or easy bruising.

The key findings on physical examination of a patient with chronic liver disease include sarcopenia, spider angiomata, a firm liver edge, splenomegaly, palmar erythema and parotid enlargement. Signs of decompensated cirrhosis are more obvious, such as ascites, jaundice and hepatic flap.

Approach to testing

The gold standard test for diagnosis of cirrhosis has been liver biopsy, however, due to its invasiveness, rare but serious complications and cost, it is now used less frequently. Nowadays, careful clinical assessment, biochemical markers and imaging can provide a reliable evaluation of a patient with cirrhosis.

Biochemical markers

The term 'liver function tests' is commonly used to group the biochemical parameters:

- aspartate aminotransferase (AST)
- alanine aminotransferase (ALT)
- gamma-glutamyl transferase
- alkaline phosphatase.

There can be an excessive focus on these tests when investigating for the presence of liver disease. While alterations in liver function tests can provide clues to the aetiology of chronic liver disease, synthetic function is more specific for detecting the presence and severity of cirrhosis.

Aminotransferases (AST and ALT) can be moderately elevated in chronic liver disease, but are often normal in advanced cirrhosis. Usually, ALT is higher than AST,

but if alcohol is the main contributor to cirrhosis, this ratio can be reversed with the concentration of AST being over twice that of ALT.

Alkaline phosphatase is often elevated in cirrhosis. Higher concentrations are seen in patients with cirrhosis secondary to cholestatic disease, such as primary sclerosing cholangitis and primary biliary cholangitis.

Gamma-glutamyl transferase is also raised in cholestatic liver disease but is less specific. The most significant confounder is alcoholic liver disease (recent or chronic alcohol ingestion) which can significantly increase the concentration.

Biochemical assessment of synthetic function is a valuable tool in screening a patient for cirrhosis. The markers of hepatic synthetic function include serum albumin and coagulation studies. The albumin concentration falls as cirrhosis progresses. However, it can be reduced in inflammatory states, malnutrition, protein-losing enteropathy or heart failure. The prothrombin time and INR are raised by impaired hepatic synthetic function. This explains the presence of coagulopathy in established liver disease. Although serum bilirubin can be normal in compensated cirrhosis, a rising concentration correlates with disease progression.

Haematological markers

A sensitive marker of cirrhosis is thrombocytopenia. This is secondary to splenic sequestration and congestive splenomegaly resulting from portal hypertension. A platelet count of less than 150 x 10^9/L is often the first marker of cirrhosis, but other cytopenias emerge as the disease progresses.

Tests for fibrosis

There are several tests that combine serum and clinical parameters to predict the presence of cirrhosis. Indirect serum fibrosis tests include the AST:ALT ratio, the AST to platelet ratio index (APRI score) and, in non-alcoholic fatty liver disease (NAFLD), the FIB-4 and NAFLD fibrosis score. The normal AST:ALT ratio is less than 1, so a score greater than 1 is suggestive of advanced fibrosis or cirrhosis.

The APRI score is validated in chronic viral hepatitis. An APRI score greater than 1 has a sensitivity of 76% and specificity of 72% for predicting cirrhosis.[2]

The FIB-4 is a combination of age, AST and platelet count, whereas the NAFLD fibrosis score is a composite of age, body mass index, presence or absence of diabetes, serum aminotransferase concentrations, platelet count and serum albumin. These scores are useful for ruling out the presence of advanced fibrosis with negative predictive values over 90%.[3]

Proprietary tests for fibrosis include the Fibrotest, the Enhanced Liver Fibrosis score (ELF), Fibrospect II and Hepascore, which was developed in Western Australia.[1] These composite scores use a range of clinical parameters and specialised serum markers, some of which are only available in tertiary referral centres.

Ultrasound

Abdominal ultrasound is generally the first imaging modality recommended when liver disease is suspected. It is widely available, low cost and has good sensitivity in excluding biliary obstruction. Features suggestive of cirrhosis on ultrasound include a nodular liver edge, splenomegaly, portal vein dilatation and recanalisation of the umbilical vein. Limitations include overlooking mild hepatic steatosis (<2.5–20%).

Elastography

Elastography is a relatively new, but now widely used imaging modality to non-invasively estimate liver stiffness. Increased liver stiffness correlates with more advanced fibrosis. Elastography does not determine the cause of cirrhosis, but by measuring the propagation speed of mechanical waves through liver parenchyma, it can give a measure of liver stiffness. Elastography is available in conjunction with ultrasound assessment in many radiology practices across Australia, or as FibroScan in most tertiary referral centres.

There are two different kinds of elastography techniques, based on ultrasound or MRI. Ultrasound generates shear waves that travel through the liver tissue at a speed determined by tissue stiffness. The faster the speed, the higher the liver stiffness. In elastography using MRI, mechanical vibration produces waves in the liver that are converted to a tissue stiffness map. This technique is not yet widely available in Australia due to its cost.

Transient elastography, known by its proprietary name FibroScan (Echosens) is the most commonly used form of elastography. It is a one-dimensional form of shear-wave elastography that measures stiffness in kilopascals (kPa). Results range from 2.5–75 kPa, with a normal value of approximately 5 kPa. Cut-offs for the severity of fibrosis (F0–F4) vary depending on the aetiology of liver disease and are best validated in chronic viral hepatitis. In stage 2–3 fibrosis the stiffness is 7–11 kPa and in stage 4 fibrosis (cirrhosis) it is more than 11–14 kPa. Limitations of FibroScan include its low reliability in patients with obesity, ascites and artificially elevated stiffness due to severe liver inflammation or steatosis.[4]

Liver biopsy

Liver biopsy is rarely needed for the diagnosis of cirrhosis, but still has a role in the definitive diagnosis of the underlying cause of liver disease. It is performed percutaneously with ultrasound guidance after confirming that there is no significant coagulopathy.

A trans-jugular liver biopsy, performed in a tertiary referral centre, is safer in patients with an increased risk of bleeding. It also enables measurement of the hepatic vein pressure gradient which is the most accurate measure of portal hypertension, but this is mainly used in research rather than clinical practice.

Monitoring

Once the diagnosis of cirrhosis is made, monitoring for deteriorating liver function or complications is important. This includes referral to a gastroenterologist for consideration of gastroscopy to look for oesophageal varices. These develop as a complication of portal hypertension and are a major cause for mortality in patients with cirrhosis. Pre-emptive treatment of varices with a non-selective beta blocker or band ligation reduces the risk of bleeding and morbidity.

Patients with cirrhosis should have surveillance for hepatocellular carcinoma. Guidelines recommend six-monthly abdominal ultrasound to detect the presence of a new liver lesion and urgent referral to a hepatologist if hepatocellular carcinoma is suspected. Measuring alpha-fetoprotein is no longer recommended as a screening test. Hepatocellular carcinoma is usually asymptomatic until it is very advanced, so surveillance enables earlier diagnosis, better treatment options and improved survival.

Specialist referral

Referral to a hepatologist should be considered for the assessment of all patients with liver cirrhosis, when the diagnosis of chronic liver disease is uncertain and for the management of complications. Patients with early, or well-compensated cirrhosis have a good prognosis, particularly if the underlying liver disease is controlled, by treatment of chronic hepatitis B or C or lifestyle modification, such as alcohol cessation. Early intervention can stabilise disease progression and help to avoid or delay hepatic decompensation.

Conclusion

The prevalence of cirrhosis is increasing. Patients are likely to have a better prognosis if there is an early diagnosis.

Making the diagnosis requires a clinical suspicion of liver disease, particularly in at-risk populations. The initial investigations include biochemical tests and imaging. Serum markers and clinical features can be combined to predict the presence of liver fibrosis. Liver fibrosis can also be assessed by measuring the tissue stiffness with elastography. Biopsy is now rarely used for the diagnosis of cirrhosis. <

Conflicts of interest: none declared

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DIAGNOSTIC TESTS

Investigating thyroid nodules

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SUMMARY

Thyroid nodules are common clinically and even more common as an incidental finding during ultrasonography. Routine screening of thyroid nodules in patients with hyperthyroidism or hypothyroidism without risk factors for thyroid cancer is not recommended.

Most thyroid nodules are benign. Sonographic risk-stratification systems should be used to estimate the risk of malignancy and the need for fine-needle aspiration biopsy.

Malignant thyroid nodules require surgical management. Most thyroid cancers are well-differentiated papillary or follicular thyroid neoplasms, which have an excellent prognosis with a low mortality rate.

Introduction

Clinically apparent thyroid nodules are present in approximately 5% of the adult population. In contrast, a far greater number of individuals are found to have incidental thyroid nodules on imaging performed for indications unrelated to the thyroid. Up to 68% of asymptomatic individuals without a history of thyroid disease who have undergone a screening thyroid ultrasound have been found to have a thyroid nodule ranging in size from a few millimetres to more than 1 cm.[1] Nodules are more common in women, the elderly and in areas of iodine deficiency.[2,3] Patients and doctors are often concerned that the nodules could be malignant.

Only 5–13% of nodules harbour thyroid cancers.[4] Factors that increase the risk of malignancy are shown in the Box. Nodules that harbour thyroid cancer are often asymptomatic.

Worldwide, the incidence of thyroid cancer has been rising over the last few decades, reflecting the increasing use of medical imaging. However, the mortality has not risen significantly. In Australia it is estimated that 73% of thyroid cancer diagnoses in 2012 represented overdiagnoses. These individuals would never have developed symptomatic thyroid cancer in their lifetime.[5]

Well-differentiated thyroid neoplasms arise from follicular cells. These papillary and follicular carcinomas account for more than 90% of all cases.[2] Medullary and anaplastic thyroid cancers are rare.[6,7]

Differentiated thyroid cancer has an excellent prognosis. Despite the presence of lymph node metastases in 5–20% of patients and distant metastases in 10–15%, the 10-year survival is 80–95%.[8] This low mortality rate is supported by the incidental finding of differentiated thyroid cancer at autopsy in approximately 10% of individuals who died from other causes and did not have a history of thyroid disease.[9]

Investigating nodules

Given the high prevalence of incidental thyroid nodules and the low prevalence of thyroid cancers, some of which may never become clinically relevant within the individual's lifetime, routine screening for thyroid nodules is not recommended in people without risk factors for thyroid cancer.[10,11] In people with a detected thyroid nodule, a stepwise approach is required to determine whether the nodule is hyperfunctioning and whether it is malignant (Fig.).

The presence of multiple thyroid nodules or a multinodular goitre does not increase the risk of thyroid cancer. The recommended approach is to assess each nodule separately for the presence of high-risk sonographic features that would suggest malignancy.[2]

History and examination

The presence of risk factors and clinical features of thyroid cancer (Table 1) should be sought. However, the history is rarely helpful in differentiating benign and malignant nodules, except if there is a history of irradiation of the head and neck in childhood. This is the greatest risk factor for thyroid malignancy as the risk of carcinoma in nodules in this group is 35–40%.[12]

Laboratory testing

Measuring thyroid-stimulating hormone is helpful. A suppressed concentration suggests that a nodule is likely to be hyperfunctioning. This should be confirmed with a technetium (Tc-99m) pertechnetate uptake scan (Fig.).[13] These scans are not indicated for assessing a nodule in patients who are euthyroid or hypothyroid. Hyperfunctioning nodules are almost never malignant.[7]

Testing for thyroid peroxidase antibodies, thyroglobulin antibodies or serum thyroglobulin is not indicated as these tests do not aid the diagnosis.[13] Thyroid-stimulating hormone receptor antibodies or thyroid-stimulating immunoglobulins can be

 This article is peer-reviewed

measured to assess for the presence of Graves' disease in patients with hyperthyroidism.[14]

Measurement of serum calcitonin to check for medullary thyroid cancer is not recommended in routine clinical practice given the high risk of false-positive results. This reflects the low prevalence of medullary thyroid cancer in thyroid nodules (0.1–1.4%).[2,15] Measurement can be considered in patients who have a family history of medullary thyroid cancer or multiple endocrine neoplasia type 2. However, it should be noted that hypercalcitoninaemia is not pathognomonic of medullary thyroid cancer and there are numerous other causes including certain drugs and chronic autoimmune thyroiditis.[2,15,16]

Ultrasound

Dedicated thyroid ultrasound (including evaluation of anterior cervical lymph nodes) is indicated to evaluate palpable thyroid nodules or those found incidentally on imaging performed for other indications. Thyroid ultrasound is not warranted to screen for nodules in individuals who have hypothyroidism or hyperthyroidism in the absence of risk factors or clinical features of thyroid cancer (Box).[10]

Risk stratification

No single sonographic feature can reliably differentiate benign from malignant neoplasms. Furthermore, there is variability between the recognition and accurate reporting of these features.[17] This has led to the development of standardised thyroid nodule risk-stratification systems such as the American College of Radiology Thyroid Imaging, Reporting and Data System (ACR TI-RADS). This system is superior to other major risk-stratification systems for evaluating thyroid nodules, because it reduces the number of unnecessary biopsies and has a high negative predictive value.[18]

The ACR TI-RADS assigns points based on five key aspects of the thyroid nodule. The total number of points categorises the nodule into five levels of increasing risk (TR1–5). Features that are suggestive of thyroid cancer (e.g. more than 90% of the nodule has a solid composition, hypoechogenicity, taller-than-wide shape on transverse view, irregular margins, microcalcifications) result in the nodule being assigned more points. In contrast, nodules with benign features (e.g. purely cystic and spongiform nodules) score fewer points. The size of the nodule in conjunction with the risk score guides the recommendation for cytological evaluation (Table 1).

There are other thyroid nodule risk-stratification systems, such as the American Thyroid Association (ATA) guideline. This also categorises nodules into five levels of risk, but smaller and lower risk nodules are recommended for biopsy, in contrast to ACR TI-RADS.[2] All the major risk-stratification systems generally do not recommend biopsy for nodules that are below 1 cm in size in the absence of high-risk features, such as suspicious cervical lymphadenopathy.[2,18]

Monitoring

Nodules that do not meet the criteria for biopsy may require re-imaging at periodic intervals to check for new suspicious sonographic changes or growth (≥20% increase in at least two nodule diameters of ≥2 mm, or ≥50% increase in nodule volume).[17] Nodules that exhibit these changes should be referred for cytological evaluation.

There is little consensus about the best interval for repeat ultrasonography or duration of follow-up. The ACR TI-RADS recommends that nodules above a certain size threshold (Table 1) be imaged again at certain intervals, assuming that there are no changes between serial ultrasound scans. TR3 nodules are recommended for repeat ultrasound at one, three and

Box Risk factors and clinical features of cancer within a thyroid nodule [7,13]

Risk factors for thyroid cancer

Radiation exposure:

- external beam radiation, especially as a child or adolescent (e.g. treatment of head and neck cancer, whole body irradiation for bone marrow transplantation)
- occupational exposure
- exposure to ionising radiation after a nuclear explosion

Personal history of thyroid cancer

Family history of thyroid cancer in a first-degree relative

Personal or family history of benign or malignant tumours suggestive of thyroid cancer syndromes:

- breast cancer e.g. Cowden syndrome
- colon cancer e.g. Cowden syndrome, familial adenomatous polyposis, Werner syndrome
- hyperparathyroidism, phaeochromocytoma e.g. multiple endocrine neoplasia type 2
- harmatomas (skin, tongue/mucosal small nodules) e.g. Cowden syndrome
- skin freckling (multiple lentigines) e.g. Carney complex type 1

Age <20 or >70 years

Features on history

Enlarging thyroid nodule*

Recent onset of hoarseness

Dysphagia*†

Anterior neck discomfort*

Features on examination

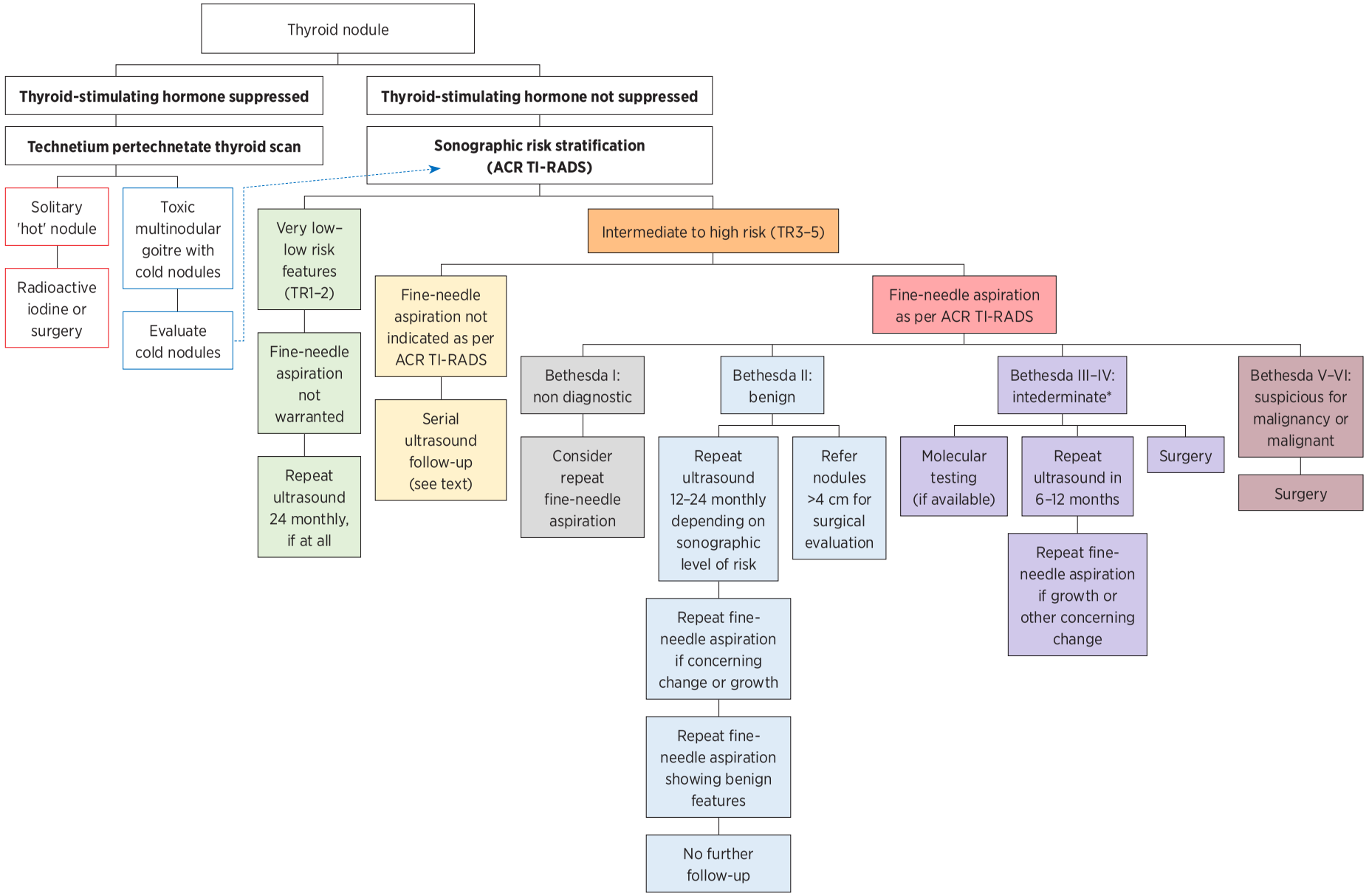
Firm, immobile thyroid nodules

Cervical lymphadenopathy (especially if ipsilateral, large, firm nodes)

Hoarseness

* These features can also occur with a benign nodule. Haemorrhage into a benign thyroid nodule or cyst can cause rapid enlargement and pain.
† Nodules that cause dysphagia would be located close to the cervical oesophagus.

Fig. **Algorithm for evaluating thyroid nodules** [7]



ACR TI-RADS = American College of Radiology Thyroid Imaging, Reporting and Data System TR = TI-RADS level of risk

* There is no clear approach. Shared decision making may take into account the molecular testing results (if available) and patient preference.

five years, TR4 nodules at one, two, three and five years. Annual scans of TR5 nodules are recommended for five years. The ACR TI-RADS does not recommend re-imaging of TR1–2 nodules or smaller TR3–5 nodules (TR3 nodule <1.5 cm, TR4 nodule <1 cm, TR5 nodule <0.5 cm) (Table 1).[19] Clinicians may consider re-imaging of TR1–2 nodules at 24-month intervals and the smaller TR3–5 nodules at 12–24-month intervals.[2,17] Routine follow-up of purely cystic or spongiform nodules of 1 cm or less is not recommended.[2,4]

The recommended duration of long-term follow-up of nodules that remain stable and continue to display low-risk features on serial sonographic assessment is five years, as these nodules have a very low risk of harbouring an undiagnosed malignancy.[19,20] Nodules that have not met the criteria for biopsy after five years of ultrasound surveillance, but still have suspicious features, such as TR3–5 nodules, may be considered for further evaluation or ongoing surveillance.[19] This should be judged on an individual basis, taking into consideration the characteristics of the nodule, patient's age and comorbid conditions.

Ultrasound-guided fine-needle aspiration

Cytological evaluation is warranted for suspicious nodules (Table 2). Thyroid nodules with increased uptake on a Tc-99m pertechnetate scan (so-called 'hot' nodules) rarely harbour a malignancy and further evaluation with a biopsy is generally not required.[7] However, the presence of suspicious sonographic features in these nodules may merit further evaluation and this should be judged on an individual basis. Suspicious cervical lymph nodes should also undergo fine-needle aspiration with a thyroglobulin washout.[2]

Samples from thyroid nodules are reported according to the Bethesda System for Reporting Thyroid Cytopathology (Table 2).[21] Approximately 15% of samples are non-diagnostic (Bethesda I), requiring clinicians to revisit the radiological characteristics to determine whether a repeat biopsy is warranted, ideally within 1–2 months.[13] Diagnostic accuracy can be improved by having an on-site pathologist available to review the adequacy of the fine-needle aspiration sample at the time of biopsy.[7]

Approximately 70% of samples are reported as having benign cytology (Bethesda II), generally indicating a low risk of malignancy. However, these results should be interpreted in conjunction with ultrasound findings. Suspicious nodules seen on ultrasound warrant follow-up within 12 months.[4] It is uncertain whether nodules that are larger than 4 cm with benign cytology are more likely to harbour a malignancy. These patients should be referred to a surgeon for consideration of further evaluation.[2,7]

Around 10–15% of samples are reported as intermediate (Bethesda III–IV). The options for further evaluation include ultrasound follow-up, repeat fine-needle aspiration, or diagnostic lobectomy.

Molecular testing for genetic alterations that convey a higher risk of malignancy are being increasingly used in the USA to help further risk stratification of nodules with indeterminate cytology.[17] However, these tests are not routinely available in Australia and are not subsidised. Several Australian centres are developing this analysis. Thyroid surgeons and endocrinologists can discuss this investigation with interested patients.

Cytology that is classified as suspicious for malignancy or malignant (Bethesda V–VI) is an indication to refer the patient to a surgeon experienced in the management of thyroid cancer.[7,13,17]

When there is uncertainty regarding further management, consultation with an endocrinologist experienced in the management of thyroid cancer is advised.

Table 1 **Risk of malignancy and criteria for fine-needle aspiration of thyroid nodules**[19]

ACR TI-RADS classification	Risk of malignancy	Criteria for follow-up*	Criteria for fine-needle aspiration
TR1 – benign	2%	Not required	Not required
TR2 – not suspicious	2%	Not required	Not required
TR3 – mildly suspicious	5%	≥1.5 cm	≥2.5 cm
TR4 – moderately suspicious	5–20%	≥1 cm	≥1.5 cm
TR5 – highly suspicious	≥20%	≥0.5 cm	≥1 cm

ACR TI-RADS = American College of Radiology Thyroid Imaging, Reporting and Data System
TR = TI-RADS level of risk
* Refer to the section on 'Monitoring' for further information.

Table 2 **Bethesda System for Reporting Thyroid Cytopathology**[21]

Bethesda category	Risk of malignancy	Comment
I – Non-diagnostic	5–10%	Insufficient sample of follicular cells or sample has degraded
II – Benign	0–3%	
III – Atypia of undetermined significance or follicular lesion of undetermined significance	10–30%	Categories III and IV reflect the inherent limitations of cytology – being unable to distinguish between benign versus malignant follicular patterned lesions given the inability to analyse the tissue architecture
IV – Follicular neoplasm or suspicious of a follicular neoplasm	25–40%	
V – Suspicious of malignancy	50–75%	Subtle or focal features of malignancy within the sample
VI – Malignant	97–99%	

SELF-TEST QUESTIONS

True or false?

4. Patients with a hot thyroid nodule require immediate referral for fine-needle aspiration to exclude a thyroid neoplasm.

5. During pregnancy an enlarging thyroid nodule requires investigation with a technetium pertechnetate scan to exclude hyperfunction.

Answers on page 209

Management

The initial management for confirmed thyroid cancer is surgical, with a total (or near-total) thyroidectomy with or without dissection of the anterior cervical lymph nodes. A lobectomy may be offered in certain low-risk cancers or microcarcinoma (diameter <1 cm).[2]

Surgery is recommended for multinodular goitres that are causing compressive symptoms. Hyperfunctioning thyroid nodules can be treated with surgery or radioactive iodine ablation.[2] Hypothyroidism should be appropriately treated.

Thyroxine suppressive therapy to retard nodule growth is not recommended. It has not been shown to be effective and is associated with an increased risk of cardiac arrythmia and osteoporosis.[2]

Pregnancy and thyroid nodules

During pregnancy, thyroid nodules generally tend to enlarge with gestational age. This does not necessarily mean that a nodule is malignant. Nodules detected during pregnancy should undergo the standard evaluation processes, except for a Tc-99m pertechnetate thyroid uptake scan as this is contraindicated in pregnancy. Women who are diagnosed with differentiated thyroid cancer during pregnancy are often able to have their surgery safely postponed until after delivery.[2]

Conclusion

Thyroid nodules are a common clinical finding, often presenting incidentally during radiology performed for the investigation of non-thyroidal illness. While most thyroid nodules are benign, all patients should undergo a stepwise evaluation. This includes with sonographic characterisation and, when indicated, cytological evaluation to determine the likelihood of underlying malignancy. Individuals diagnosed with thyroid cancer should be referred for surgical management. <

Conflicts of interest: none declared

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FURTHER READING

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FEATURE

Top 10 drugs 2020–21

Aust Prescr 2021;44:205
https://doi.org/10.18773/austprescr.2021.062

Tables 1–3 show the top 10 drugs for the year July 2020 – June 2021. The figures are based on PBS and RPBS prescriptions from the date of supply. The figures include prescriptions under the co-payment (non-subsidised).

Table 1 **Top 10 PBS/RPBS drugs by DDD/1000 pop/day**

	Drug	DDD/1000 pop/day*
1.	atorvastatin	76.22
2.	rosuvastatin	66.54
3.	perindopril	54.35
4.	amlodipine	53.35
5.	candesartan	34.56
6.	telmisartan	34.55
7.	irbesartan	29.36
8.	sertraline	27.42
9.	metformin	26.59
10.	ramipril	26.52

Table 2 **Top 10 PBS/RPBS drugs by prescription counts**

	Drug	Prescriptions
1.	rosuvastatin	14,185,361
2.	atorvastatin	11,673,109
3.	pantoprazole	9,299,295
4.	esomeprazole	8,396,611
5.	perindopril	6,890,787
6.	escitalopram	5,470,158
7.	metformin	5,406,768
8.	sertraline	5,106,720
9.	cefalexin	4,617,588
10.	amlodipine	4,475,471

Table 3 **Top 10 PBS/RPBS drugs by cost to government (does not include rebates)**

	Drug	Cost to government	Prescriptions
1.	aflibercept	$443,729,600	364,846
2.	pembrolizumab	$431,701,955	49,694
3.	nivolumab	$402,113,073	50,593
4.	adalimumab	$297,594,138	274,986
5.	denosumab	$263,487,070	963,893
6.	apixaban	$248,455,067	3,020,507
7.	ustekinumab	$246,990,067	35,554
8.	ranibizumab	$221,730,401	190,316
9.	lenalidomide	$221,365,364	40,554
10.	ocrelizumab	$175,644,997	10,108

DDD definied daily dose

PBS Pharmaceutical Benefits Scheme

RPBS Repatriation Pharmaceutical Benefits Scheme

* DDD/thousand population/day is a more useful measure of drug utilisation than prescription counts. It shows how many people in every thousand Australians are taking the standard dose of a drug every day. DDD includes use in combination products. The calculation is based on ABS 3101.0 – Australian Demographic Statistics for December 2020.

Source: Department of Health, December 2021. © Commonwealth of Australia

FEATURE

Medicines Australia Code of Conduct: breaches 2020–21

Keywords
Medicines Australia, codes of conduct, drug industry

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The Medicines Australia Code of Conduct guides the promotion of prescription products by pharmaceutical companies.[1] The 19th edition of the Code of Conduct came into effect in March 2020. Throughout the year Medicines Australia publishes reports, from its Code of Conduct Committee, on the successful complaints about advertising and other promotional activities.

In 2020–21 the Code of Conduct Committee finalised four complaints (see Table).[2,3] These were dealt with under the 18th and 19th editions of the Code of Conduct.[1] All the complaints were made by pharmaceutical companies. Details of each complaint are available on the Medicines Australia website.[2,3]

Table **Breaches of the Code of Conduct July 2020 – June 2021**

Company	Brand (generic) name	Material or activity	Sanction
Boehringer Ingelheim/ Eli Lilly Australia Alliance*	Jardiance (empagliflozin)	Presentations to meetings of healthcare professionals	Withdraw presentation, corrective letter, $150,000 fine
Novartis*	Beovu (brolucizumab)	Promotional material	Cease using material, corrective letter, $200,000 fine. Fine confirmed on appeal
AstraZeneca †	Forxiga (dapagliflozin propanediol monohydrate) Xigduo XR (dapagliflozin propanediol monohydrate/ metformin hydrochloride) Qtern (saxagliptin/dapafliglozin)	Promotional material	Withdraw material, corrective letter, $100,000 fine
AbbVie ‡	Rinvoq (upadacitinib)	Promotional material	Cease and withdraw material, $125,000 fine. Fine upheld on appeal

* Complaint heard under 18th edition of the code
† Complaint heard under 19th edition of the code
‡ Complaint heard under 18th and 19th editions of the code

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New drugs

Axicabtagene ciloleucel

Aust Prescr 2021;44:207
https://doi.org/10.18773/austprescr.2021.058
First published 27 October 2021

Approved indication: B-cell lymphoma

Yescarta (Gilead)
cryostorage bag containing 1 x 10^6 – 2.4 x 10^6 cells/kg suspension for infusion.

The large B-cell lymphomas are a common type of non-Hodgkin lymphoma. Although treatment can cure many patients, those with refractory or relapsed disease have a poor prognosis. The median survival is approximately six months. Current salvage regimens are not very effective so other therapies are being investigated.

Many B-cell cancers express the CD19 antigen, so this has become a target for immunotherapy. Chimeric antigen receptor (CAR) T-cell therapy is one approach. The patient's own T cells are collected by leukapheresis. They are then genetically engineered to recognise the CD19 antigen. Large numbers of these anti-CD19 CAR T cells are produced then infused back into the patient.

Axicabtagene ciloleucel is a CAR T-cell therapy that, on binding to the CD19 antigen, has cytolytic activity and stimulates T-cell proliferation and the release of cytokines. The concentration of T cells peaks within 7–14 days of infusion. Cytokines and chemokines also peak within 14 days with concentrations returning to normal within 28 days.

The efficacy of axicabtagene ciloleucel was assessed in a phase II trial involving patients with refractory disease. Most had diffuse large B-cell lymphoma, but patients with primary mediastinal B-cell lymphoma or transformed follicular lymphoma were also included. All the patients were given chemotherapy a few days before the infusion of axicabtagene ciloleucel. A total of 101 patients were treated. When evaluated at least six months after the infusion, the objective response rate was 82% with 54% being complete responses. After a median follow-up of 15.4 months there was still a response in 42% of the patients. The median duration of the response was 8.1 months.[1]

The 101 patients were evaluated again after a median follow-up of 27.1 months. By then 61 patients had died or had progressive disease. The objective response rate was 83% with 58% having had a complete response. The median duration of the response was 11.1 months, with the median progression-free survival being 5.9 months. While median overall survival could not be calculated, the estimated two-year survival was 50.5%.[2]

The patients in the phase II trial had already received at least two treatments and were given lymphodepleting chemotherapy before being infused with axicabtagene ciloleucel. They all experienced adverse events which were at least grade 3 (severe) in 95%. The most frequent adverse events were fever, neutropenia, anaemia, thrombocytopenia and hypotension.[1] As axicabtagene ciloleucel causes cytokine secretion, most patients will develop a cytokine-release syndrome. This emerged in a median of two days and persisted for a median of eight days after the infusion. The deaths of two of the 101 patients were associated with the cytokine-release syndrome.

Axicabtagene ciloleucel should not be given to patients with active inflammation or infection. The therapy is also neurotoxic. Many patients will experience toxicities, such as encephalopathy, within a week of the infusion. Common presentations include confusion, tremor and aphasia.[1] CAR T-cell therapy places patients at risk of infection. As CD19 is found on normal B cells, some patients develop B-cell aplasia and hypogammaglobulinaemia. During the phase II trial 35% of the patients developed febrile neutropenia.[1]

It is still early days in the evolution of CAR T-cell therapy. On the data available so far, the response rate of 82% for axicabtagene ciloleucel in refractory disease is higher than the response rate of 20% seen in historical controls.[1] A favourable response is more likely in patients with high numbers of anti-CD19 CAR T cells, but it is not yet known if this will result in longer overall survival or improve the quality of life.[2]

T manufacturer provided the product information

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The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, and the European Medicines Agency.

The new drug commentaries in *Australian Prescriber* are prepared by the Editorial Executive Committee. Some of the views expressed on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

NEW DRUGS

Niraparib

Aust Prescr 2021;44:208–9
https://doi.org/10.18773/austprescr.2021.059
First published 27 October 2021

Approved indication: ovarian cancer

Zejula (GlaxoSmithKline)
100 mg capsules

Ovarian cancer often presents late and tends to recur despite chemotherapy. This has led to a search for maintenance treatments for women with recurrent cancer. One approach is to inhibit the enzymes involved in the repair of DNA in tumour cells. In vitro, inhibition of the poly (ADP-ribose) polymerase (PARP) enzymes is cytotoxic and reduces tumour growth. Olaparib is a PARP inhibitor that has been used in ovarian cancer, but its efficacy is in tumours with mutations of the BRCA genes. Niraparib is a PARP inhibitor that may have efficacy in a wider range of tumours.

Patients start treatment within eight weeks of completing a course of chemotherapy. The recommended dose of niraparib is 300 mg once daily. Food does not significantly affect absorption. Most of the dose is metabolised with the metabolites being excreted in urine and faeces. This metabolism does not involve the cytochrome P450 system and there have been no drug–drug interaction studies. The half-life of niraparib is 36 hours, but it is unknown if this and other pharmacokinetic parameters are affected by severe kidney disease or moderate–severe hepatic impairment.

An open-label phase II treatment trial enrolled 463 women who had received a median of four chemotherapy regimens for ovarian, fallopian tube or primary peritoneal cancer. Most of these relapsed cancers had become resistant or refractory to platinum therapy. The patients took niraparib 300 mg daily with a median follow-up of 12.2 months. There was a response to treatment in 8% (38/456) of the women. The response rates varied with the genetics of the tumours. Overall survival was 17.2 months, but it was 26 months if there was a BRCA mutation.[1]

The phase III NOVA trial of maintenance therapy enrolled 553 women with cancer of the ovary, fallopian tube or peritoneum. Despite sensitivity to platinum-based chemotherapy, the cancer had progressed. A BRCA mutation was present in 203 women. The patients were randomised in a 2:1 ratio to daily niraparib or a placebo and followed up for a median of 16.9 months. In the women who had BRCA mutations, the median progression-free survival was 21 months with niraparib and 5.5 months with placebo. The corresponding figures were 9.3 months and 3.9 months for the 350 women without a mutation.

The actions of niraparib are not confined to cancer cells so all patients will experience adverse effects. In the NOVA trial 14.7% of patients given niraparib had to stop treatment because of adverse effects compared with 2.2% of the placebo group.[2] As niraparib suppresses bone marrow, patients are at risk of anaemia, thrombocytopenia and neutropenia. These adverse effects may require treatment to be reduced or stopped, so the blood count should be regularly checked. In the NOVA trial 1.4% of the women taking niraparib developed myelodysplastic syndrome. Regular monitoring should also include pulse and blood pressure. Severe hypertension, including hypertensive crisis, affected 8.2% of the patients in the NOVA trial compared with 2.2% of the placebo group. Other adverse effects that are more frequent with niraparib than placebo include nausea, vomiting, constipation, fatigue, dyspnoea, mucositis and insomnia. Despite these common problems, the NOVA trial reported that the quality of life was similar for patients given niraparib or placebo.[3]

On the evidence to date, niraparib has been approved as maintenance therapy for women with platinum-sensitive, relapsed high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer who have had a complete or partial response to platinum-based chemotherapy. However, it is currently uncertain if the advantage of niraparib over placebo in progression-free survival will lead to a confirmed improvement in overall survival. When the NOVA trial was published, 16.1% of patients given niraparib had died compared with 19.3% of the placebo group.[2] Further research will be needed to identify which women are most likely to benefit from a PARP inhibitor. A phase II trial has reported that progression-free survival is greater if niraparib treatment is combined with bevacizumab, compared to niraparib alone (median 11.9 vs 5.5 months).[3] Niraparib maintenance therapy has also been found to improve progression-free survival compared to placebo (median 13.8 vs 8.2 months) in a phase III trial involving women with newly diagnosed advanced ovarian cancer.[4]

[X] manufacturer did not respond to request for data

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The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, and the European Medicines Agency.

A:

ANSWERS TO SELF-TEST QUESTIONS

1 True
2 True
3 True
4 False
5 False

Correction

The safety of commonly used vitamins and minerals [Correction]

Aust Prescr 2021;44:209
First published 5 November 2021
https://doi.org/10.18773/austprescr.2021.060

The article on the safety of vitamins and minerals (Aust Prescr 2021;44:119-23) has been corrected. View corrected article.

In the 'Vitamin A' section of the main text, it incorrectly states that toxicity can occur with regular ingestion of more than 100,000 IU daily. This should read "Vitamin A toxicity can occur with regular ingestion of more than 10,000 IU daily". The information on vitamin A toxicity in Box 1 is correct.

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