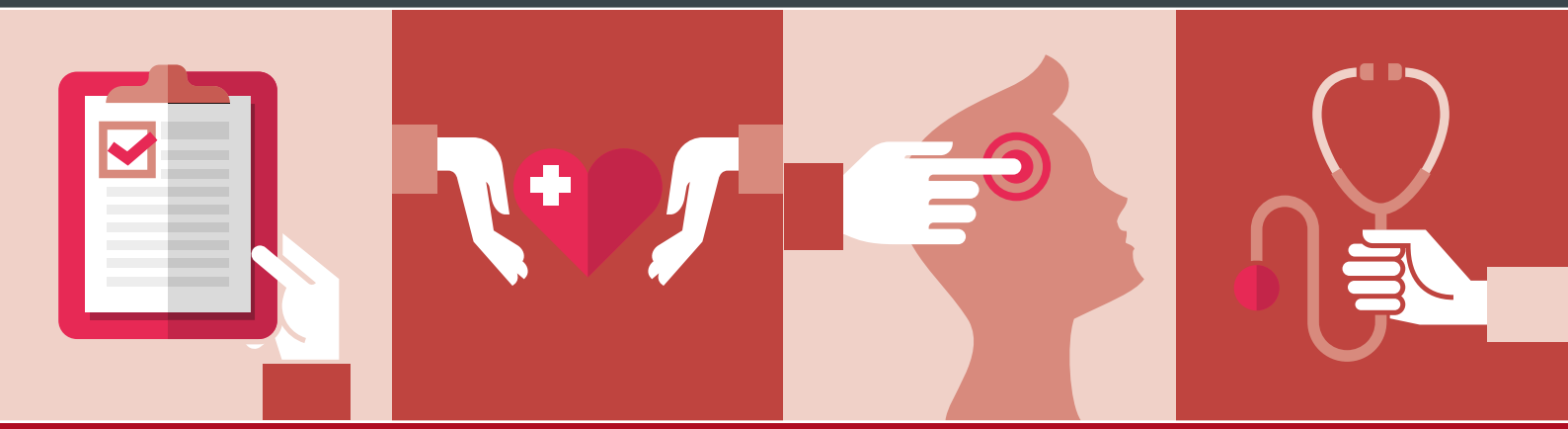
check

Independent learning program for GPs



Unit 526 April 2016

Blood disorders

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Need to know more about iron deficiency anaemia?

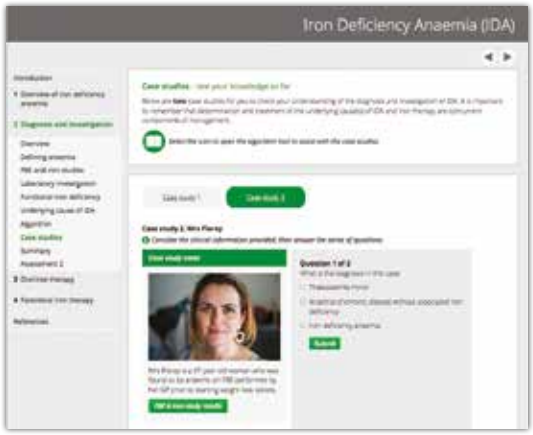
There were 42,466 potentially preventable hospitalisations for Iron Deficiency Anaemia (IDA) in Australia in 2013–14.

Go to ›

www.bloodsafelearning.org.au › **Resource Centre** ›

Resources:

- IV iron administration in primary care video
- IV iron tools
- IDA course
  - Free to access
  - RACGP endorsement and CPD points
- IDA app
  - Algorithm to assist with diagnosis, investigation and management
  - Free download



IDA course

Primary care video

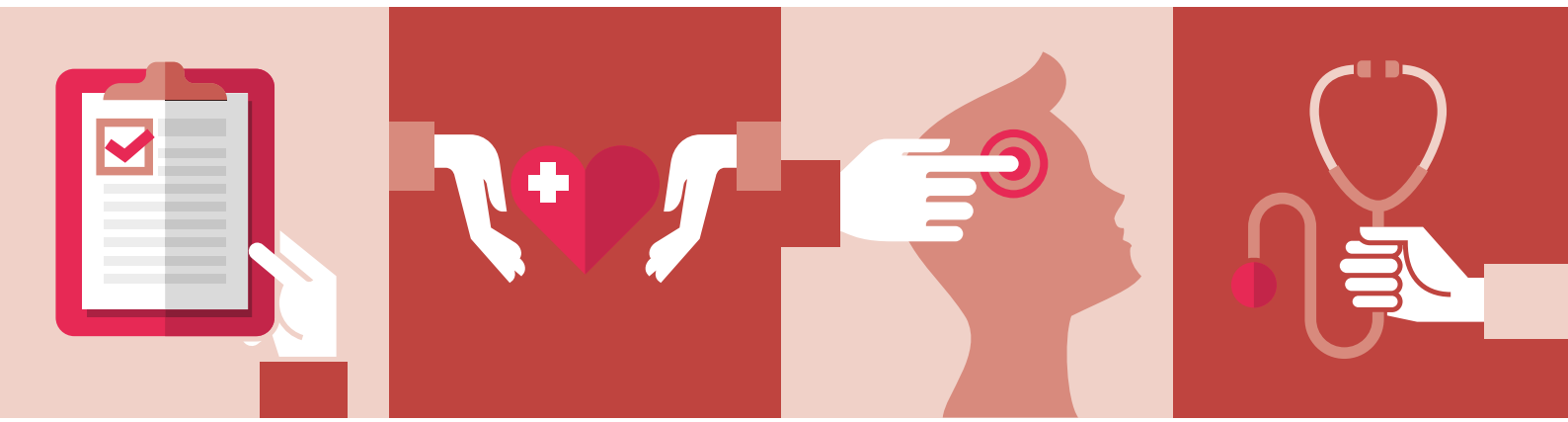
IDA app

ANDROID APP ON Google play

Available on the App Store

BloodSafe
eLearning Australia

check
Independent learning program for GPs



Blood disorders

Unit 526 April 2016

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The five domains of general practice

- Communication skills and the patient–doctor relationship
- Applied professional knowledge and skills
- Population health and the context of general practice
- Professional and ethical role
- Organisational and legal dimensions

RACGP

FIT FOR SURGERY
FIT FOR LIFE

IRON DEFICIENCY: THE FACTS

About 1 in 10 people in Australia have low iron levels also called iron deficiency

3 in 10 people having elective surgery have low iron or anaemia – this puts you at a much higher risk of transfusion.

CAUSES OF ANAEMIA

- Chronic disease
- Blood loss
- Dietary deficiency (iron, B12)
- Gastrointestinal problems

WHY IS IRON IMPORTANT?

You need iron to make haemoglobin. Haemoglobin carries oxygen from your lungs to your body.

If left untreated low iron levels and anaemia can:

- delay your surgery.
- increase your chance of needing a blood transfusion.
- increase your chance of complications.
- slow down your recovery after surgery.

Having anaemia before you go in for surgery puts you at a higher risk of needing a blood transfusion.

Blood is a precious commodity and should not be used lightly.

A blood transfusion is an organ transplant and comes with inherent risks.

RESOURCES AVAILABLE INCLUDE

More information and to download resources visit: www.blood.gov.au or www.nps.org.au/topics/surgery

NATIONAL BLOOD AUTHORITY AUSTRALIA

NPS MEDICINEWISE

ABOUT THIS ACTIVITY

As the first port of call for most Australians seeking healthcare, general practitioners (GPs) need to know how to assess, diagnose and manage patients with, or who are suspected of having, a variety of conditions and disorders. With the complexities of blood conditions and diseases, GPs are likely to see more of these patients presenting to their practice.

Atrial fibrillation is a major risk factor for strokes, which can be associated with high rates of morbidity and mortality.[1] In many cases, strokes can be prevented by identification of patients at risk and timely initiation of anticoagulant therapy.[1] Warfarin has been commonly used for reducing stoke risk, but newer oral anticoagulants are now also available. As hyperthyroidism has been found to be associated with a decreased response to anticoagulants such as warfarin,[2] GPs need to monitor patients with thyroid dysfunctions who are receiving anticoagulants. *HFE*-associated hereditary hemochromatosis (*HFE*-HH) is characterised by an excess of ferritin, an iron storage protein, in the blood and tissues of the body.[3] Patient blood management is especially important when a patient has to undergo surgery or invasive procedures and involves conserving a patient's own blood in the event of significant blood loss.[4]

Infections and deaths from diseases such as hepatitis B and C are increasing in Australia,[5,6] where an estimated 225,000 Australians are chronically infected with hepatitis, and nearly half undiagnosed.[7,8]

This edition of *check* considers the management and treatment of various blood-related conditions that may present in general practice.

LEARNING OUTCOMES

At the end of this activity, participants will be able to:

- describe the assessment and management of a patient at risk of thromboembolism
- discuss the considerations related to patient blood management prior to surgery
- outline the assessment and management of a patient with hyperferritinaemia
- summarise the recommendations for diagnosis and treatment of hepatitis B
- discuss the general practitioner's role in prescribing antivirals for hepatitis C.

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ACRONYMS

ACE	angiotensin converting enzyme
AF	atrial fibrillation
AFP	alpha-fetoprotein
ALP	alkaline phosphatase
ALT	alanine aminotransferase
anti-HBc	hepatitis B core antibody
anti-HBe	hepatitis B e-antibody
anti-HBs	hepatitis B surface antibody
AST	aspartate aminotransaminase
AV	atrioventricular
BMI	body mass index
BP	blood pressure
CHB	chronic hepatitis B
CRP	C-reactive protein
DAA	directly acting antiviral
DVT	deep vein thrombosis
EASL	European Association for the Study of the Liver
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
FBE	full blood evaluation
FDA	Food and Drug Administration
GGT	gamma-glutamyl transferase
GP	general practitioner
HAV-IgG	hepatitis A virus immunoglobulin G
HbA1c	glycated haemoglobin
HBeAg	hepatitis B e-antigen
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HFE	haemochromatosis gene
HH	hereditary hemochromatosis
HIV	human immunodeficiency virus
IDA	iron deficiency anaemia
INR	international normalised ratio
IV	intravenous
LFT	liver function test
MCH	mean corpuscular haemoglobin
MCV	mean corpuscular volume
NOACs	new oral anticoagulants
NSAID	non-steroidal anti-inflammatory drug
PBM	patient blood management
PBS	Pharmaceutical Benefits Scheme
PT	prothrombin time
RDW	red cell distribution width
RNA	ribonucleic acid
SVR	sustained virological response
TFT	thyroid function test
Tg	thyroglobulin
TIA	transient ischaemic attack
TPO	thyroperoxidase
TSH	thyroid stimulating hormone
UEC	electrolytes and creatinine
VKA	vitamin K antagonist

CASE 1

KEVIN PRESENTS WITH PALPITATIONS

Kevin, 63 years of age, is a businessman who has recently returned home from overseas. His medical history is significant only for hypertension, which is managed with lisinopril. He presents to you with a four-month history of intermittent palpitations.

QUESTION 1

What components of history-taking and physical examination are important?

FURTHER INFORMATION

Kevin describes his palpitations as regular and rapid, occurring multiple times per day for up to 10 minutes in duration. They are not influenced by exercise or stress, and he has not taken any additional medications, including herbal remedies. Kevin does not drink alcohol. He has no features of myocardial ischaemia such as chest pain, but sometimes feels presyncopal. He has no personal or family history of cardiac disease or clotting disorders. He denies calf pain and swelling, and has no respiratory symptoms. On further questioning, Kevin reports several months of unintentional weight loss, heat intolerance, alopecia and diarrhoea. Kevin returned two weeks ago from a three-day business trip to New Zealand. He describes only spending time at work and in his hotel during this trip.

On examination, Kevin is a lean looking man with a BMI of 18 kg/m^2. He is tachycardic with a regular heart rate of 160 beats per minute. His blood pressure is 138/80 mmHg and his other vital signs are normal. Kevin has a prominent tremor of his outstretched hands, upper limb hyperreflexia and a diffuse, moderately enlarged, smooth, non-tender thyroid with a bruit but no palpable nodules. The remainder of the examination, including cardiorespiratory and abdominal examination, is unremarkable, specifically with no features of heart failure.

QUESTION 2

What is the likely cause of Kevin's palpitations? What are some of the important differential diagnoses of palpitations?

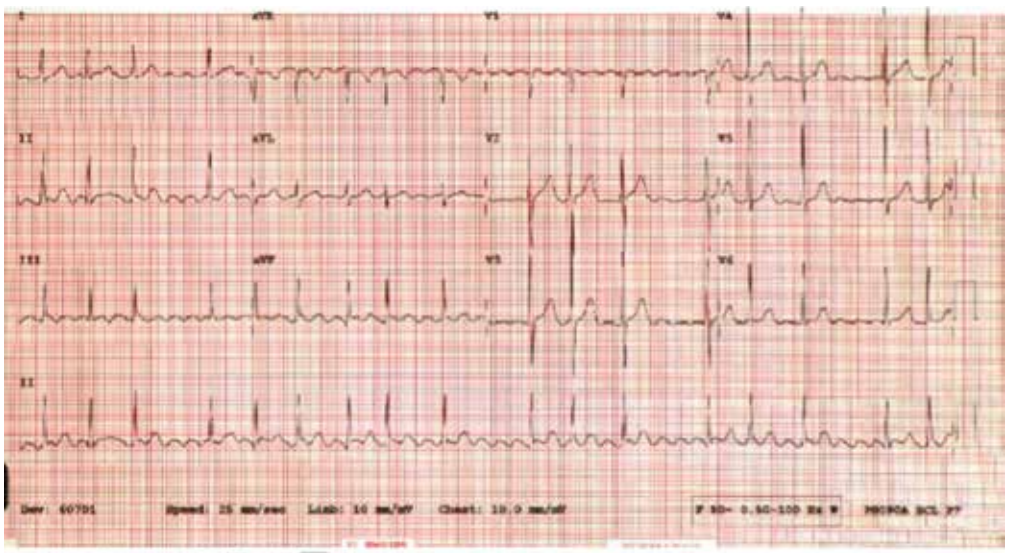
QUESTION 3

What initial investigation would you perform in your clinic?

FURTHER INFORMATION

An ECG shows atrial flutter with a rapid ventricular rate. A copy of Kevin's ECG is presented in Figure 1 (taken once the rate had been decreased somewhat).

Figure 1. Kevin's ECG trace



QUESTION 4

What is the next most appropriate course of action?

FURTHER INFORMATION

You organise for an urgent ambulance to transfer Kevin to the emergency department of the closest tertiary hospital. His clinical status is unchanged on arrival to hospital. The emergency team organise preliminary investigations including basic haematology, biochemistry and thyroid function. For immediate management of Kevin's atrial flutter, 25 mg of oral metoprolol is administered with a repeat ECG in 30 minutes.

Kevin's thyroid function tests (TFTs) are shown in Table 1. His other pathology tests are unremarkable.

Table 1. Kevin's TFT results

	Kevin's result	Reference
Free T3	23.9 pmol/L	2.4–5.9
Free T4	41.7 pmol/L	9.1–19.6
TSH	<0.01 mU/L	0.30–5.00

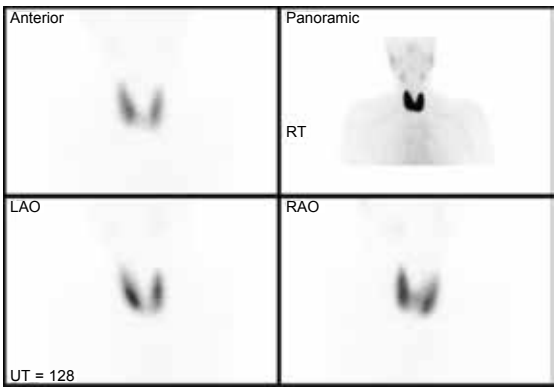
TSH, thyroid stimulating hormone

He is admitted under the endocrinology team, who organise thyroid autoantibody tests, including a thyroid stimulating hormone (TSH) receptor antibody test and a Tc-99m pertechnetate thyroid scan. Kevin's TSH receptor antibody levels are elevated at 5.4 units/L (normal <1.8 units/L) and the thyroid scan showed diffuse, increased tracer uptake (Figure 2).

QUESTION 5

How would you interpret Kevin's TFT results? What is the diagnosis?

Figure 2. Kevin's ECG trace



QUESTION 6

How should Kevin's hyperthyroidism be managed in the short term?

FURTHER INFORMATION

Kevin is commenced on carbimazole 20 mg twice daily and metoprolol 25 mg twice daily.

QUESTION 7

What duration of therapy is generally necessary for Graves' disease? How successful is it in the long term? How frequently should the TFTs be monitored?

QUESTION 8

Given the key presenting complaint in Kevin's case, what potential complications and prophylactic therapy should be considered? What factors should be considered in deciding whether to commence this prophylactic therapy in Kevin?

QUESTION 9

When considering oral anticoagulant options, what are the advantages and disadvantages of novel oral anticoagulants (NOACs), compared with warfarin? Are there any particular concerns in the context of thyroid disease?

FURTHER INFORMATION

The cardiology team review Kevin in hospital and suggest anticoagulation with warfarin. He reverts to sinus rhythm within 48 hours and is discharged. Four weeks later, his thyroid function is much improved, allowing a dose reduction of carbimazole. He remains in sinus rhythm and is currently awaiting a transthoracic echocardiogram.

QUESTION 10

How long will Kevin require anticoagulation?

CASE 1 ANSWERS

ANSWER 1

A directed history targeting possible underlying aetiologies of palpitations and potential complications should be undertaken. This should incorporate:

- history of presenting complaint
  - frequency and duration of episodes
  - nature of the palpitations – Are they fast? Are they regular or irregular?
  - precipitating factors (eg caffeine, stress, medication)
  - features suggestive of ischaemia (eg chest pain, dyspnoea, nausea)
  - symptoms suggestive of arrhythmia (eg presyncope, syncope)
  - features of hyperthyroidism (eg weight loss, tremor, diarrhoea, diaphoresis, heat intolerance)
  - features of anxiety (eg choking sensation, symptoms of depression)
  - features of phaeochromocytoma (eg paroxysmal headaches, flushing)
  - features of pulmonary embolism/deep vein thrombosis (DVT) (eg calf pain/swelling, tachypnoea, dyspnoea)
- complete medication history including use of illicit drugs and herbal remedies, and travel history
- family history of sudden cardiac death, thromboembolism, endocrine disorders such as thyroid disease
- social history including alcohol consumption.

Physical examination should focus on:

- overall impression of current clinical status
  - well or unwell
- vital signs
  - temperature, heart rate and rhythm, blood pressure, respiratory rate, oxygen saturation
- weight, height, body mass index (BMI)
- cardiorespiratory examination
  - assessment of fluid status, signs of valvular disease and cardiac failure (left-sided and right-sided), signs of pulmonary hypertension, assessment of lower limbs for possible DVT
- abdominal examination
  - signs of right-sided heart failure (eg ascites)
- thyroid examination
  - assess for signs of hyperthyroidism (eg upper limb tremor, diaphoresis, hyperreflexia, alopecia)
  - assess for potential underlying cause of hyperthyroidism (eg ophthalmopathy, diffuse non-tender enlarged thyroid with underlying bruit would suggest Graves' disease; nodular thyroid gland in the absence of above features would raise suspicion of a toxic multinodular goitre or toxic adenoma if apparently single; tender, firm thyroid in the absence of prior features would suggest thyroiditis).

ANSWER 2

The most likely cause of Kevin's palpitations is hyperthyroidism. He has features that are also suggestive of Graves' disease, including a smooth, diffusely enlarged thyroid with a bruit.

Important differential diagnoses of palpitations include:[1]

- cardiac arrhythmias
  - supraventricular/ventricular ectopic beats
  - supraventricular/ventricular tachycardias
  - bradyarrhythmias
  - anomalies in pacemaker/implantable cardioverter defibrillator (ICD) functioning
- structural heart disease
  - valvular disease
  - congenital heart diseases with significant shunt
  - cardiomyopathy
  - anxiety
  - depression
  - somatisation disorders
- systemic disorders
  - hyperthyroidism
  - hypoglycaemia
  - high output states (eg fever, anaemia)
  - phaechromocytoma

- medication
  - withdrawal of beta blockers
  - anticholinergics
  - sympathomimetic agents in pump inhalers
- lifestyle
  - caffeine
  - alcohol
  - nicotine
  - amphetamines
  - cannabis
  - cocaine
  - heroin
  - other illicit drugs.

ANSWER 3

The most appropriate initial investigation to perform in your clinic, if available, should be an electrocardiogram (ECG) to establish Kevin's heart rhythm and assess for evidence of silent myocardial ischaemia.

ANSWER 4

Given the arrhythmia, and therefore possible risk of haemodynamic compromise, it is most appropriate to transfer Kevin to an emergency department via ambulance.

ANSWER 5

The TFT results – elevated free T4 and free T3, and suppressed TSH – are consistent with hyperthyroidism. A positive TSH receptor antibody test is consistent with Graves' disease. Positive anti-thyroperoxidase (TPO) and anti-thyroglobulin (Tg) tests are non-specific, but are often elevated in autoimmune thyroid disorders. Nuclear imaging of the thyroid with a Tc-99m pertechnetate thyroid scan is useful as it can differentiate causes of hyperthyroidism, such as Graves' disease, toxic adenoma, toxic multinodular goitre and subacute thyroiditis.

ANSWER 6

Beta blockers are useful in the short term for control of palpitations while awaiting antithyroid medication to take effect.[2] Propranolol is historically the beta blocker of choice in the absence of an additional indication.[3] In this case, given that Kevin has an atrial flutter with rapid ventricular response, a ß1-selective agent such as metoprolol would be appropriate.[4]

Antithyroid medication is indicated to normalise thyroid function and either carbimazole or propylthiouracil can be used, although the former is preferred because of its superior safety profile.[2] Propylthiouracil rather than carbimazole should be used for women in the first trimester of pregnancy, as carbimazole may be more teratogenic in cases of thyroid storm and in those with allergies to carbimazole.[2] Doses of carbimazole and propythiouracil depend on the severity of thyroid dysfunction.

ANSWER 7

Patients are typically treated with antithyroid medication (carbimazole as first line) for 12–18 months to normalise thyroid function and induce remission.[2] Thereafter, antithyroid medication may be ceased, provided the patient is euthyroid on a low dose, acknowledging the relapse rate is up to 50%.[5] The presence of a goitre, persistently elevated TSH receptor antibody levels, male gender and/or an inability to wean antithyroid medication may help predict relapse. In those who experience relapse, options for ongoing management include recommencement of antithyroid medication or definitive therapy with radioiodine ablation or total thyroidectomy. Definitive treatment is favoured as a second trial of antithyroid medication, while controlling the hyperthyroidism is unlikely to result in sustained remission after drug withdrawal.

TFTs should be obtained about four weeks after commencement of anti-thyroid therapy, and dosages adjusted accordingly. Until euthyroidism is achieved, the levels should be rechecked every four to eight weeks.[6]

ANSWER 8

In the setting of atrial flutter, with likely paroxysmal episodes dating well before 24 hours before diagnosis, the risk of thromboembolism must be assessed and the use of anticoagulation considered.[4,7]

An assessment needs to be made of the patient's risk of stroke and bleeding. Most guidelines suggest the use of a validated risk score for the assessment of stroke risk, such as CHA2DS2VASc, which incorporates cardiac failure, hypertension, diabetes, sex, history of stroke and history of vascular disease.[7] It is generally recommended that an oral anticoagulant be started if the score is ≥2, and that anticoagulation is not necessary if the score = 0. There is some debate regarding recommendations for patients with a score of 1, but the European guidelines recommend oral anticoagulation or aspirin, with a stated preference for anticoagulation where possible.[7,8] With regard to bleeding risk, factors such as age, mobility, presence of hypertension, renal function, liver function and history of bleeding need to be considered. A risk score such as HAS-BLED can be used.[7]

Thyroid disease is not incorporated into these commonly used risk scores, but may be another important consideration. Excess thyroid hormone affects several coagulation and fibrinolytic parameters. In subclinical and overt hyperthyroidism, a shift of haemostasis towards a hypercoagulable and hypofibrinolytic state with a rise in factors VIII and IX, fibrinogen, von Willebrand factor, and plasminogen activator inhibitor-1 is observed.[9] Unfortunately, there are limited data on the risk of embolic stroke in patients with hyperthyroidism and atrial fibrillation/flutter. Clinicians should be aware that there may be increased risk of thromboembolism in hyperthyroidism-associated atrial fibrillation/flutter; however, there is currently insufficient evidence to quantify this risk and therefore the presence of thyroid disease has not been factored into treatment recommendations.

ANSWER 9

Despite the high prevalence of atrial arrhythmias such as atrial fibrillation (AF) and flutter, current evidence to guide decisions regarding anticoagulation in patients with these conditions and overt thyroid disease is lacking.

The recent introduction of NOACs has been welcomed by many for their fixed dosing regimen, lack of required monitoring, fast onset and offset of action, and fewer drug and food interactions.[10] Two different classes of NOACs directly targeting factor Xa and thrombin are currently available on the Pharmaceutical Benefits Scheme (PBS) in Australia for patients with non-valvular AF and at least one additional risk factor for stroke.

However, the lack of clinically validated tests to monitor NOAC effects may be detrimental in cases of altered pharmacodynamics such as hyperthyroidism. Hyperthyroidism increases the turnover of vitamin K-dependent clotting factors, which has been shown to increase patients' sensitivity to warfarin.[11] Although there is no current literature on the effectiveness of NOACs in hyperthyroidism, given their pharmacological effects are directly dependent on vitamin K-related clotting factors, it is likely that a similar effect will be observed. An antibody fragment against dabigatran, idarucizumab, has been developed.[12] However, it is expensive and not easily available in Australia. As yet, there are no reversal agents available for any of the other NOACs. On the other hand, warfarin can be reversed relatively easily and at minimal expense. Pending further research and clinical experience, warfarin may be considered the safest option due to its ease of monitoring and dose adjustment, our understanding of its pharmacodynamics in thyroid disorders, and the availability of a simple reversal agent.

ANSWER 10

There are no guidelines regarding the appropriate duration of anticoagulation in those with thyroid dysfunction and atrial fibrillation or flutter. It seems reasonable to cease anticoagulation after a sustained period of euthyroidism provided the patient has reverted to sinus rhythm and there are no other indications for anticoagulation such as valvular heart disease or prior stroke. Consultation with a cardiologist is recommended.

RESOURCES FOR PATIENTS

- Better Health Channel – Heart arrhythmias and palpitations, www.betterhealth.vic.gov.au/health/conditionsandtreatments/heart-arrhythmias-and-palpitations
- Better Health Channel – Thyroid – hyperthyroidism, www.betterhealth.vic.gov.au/health/conditionsandtreatments/thyroid-hyperthyroidism

RESOURCES FOR DOCTORS

- Therapeutic Guidelines: Cardiology – Atrial flutter and Atrial fibrillation, 2012
- Therapeutic Guidelines: Endocrinology – Hyperthryroidism, 2014
- Tran H, Joseph J, Young L, et al. New oral anticoagulants: A practical guide on prescription, laboratory testing and peri-procedural/bleeding management. Intern Med J 2014;44(6):525–36. Available at www.asth.org.au/downloads/NOAC_imj_12448.pdf

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CASE 2

MARY NEEDS A KNEE REPLACEMENT

Mary is a retired bookkeeper, aged 76 years, who was formerly very active, playing regular golf and bowls. However, she is now significantly limited in her mobility. Mary's previous history includes mild hypertension and occasional exercise-induced angina. Her medications are atenolol 50 mg daily, meloxicam 15 mg daily, paracetamol 1000 mg TDS, glucosamine 1.5 g, fish oil and glyceryl trinitrate as needed. Mary is a non-smoker and has a moderate alcohol intake.

A referral to the local public hospital for assessment of knee replacement surgery has been arranged.

QUESTION 1

What factors related to the management of a patient's blood should be considered when referring them for major surgery?

QUESTION 2

What blood tests should be performed? When and why?

FURTHER INFORMATION

An FBE shows the following results:

- haemoglobin – 116 g/L (reference range 115–160 g/L)
- mean corpuscular volume (MCV) – 81 fL (reference range 80–98 fL)
- mean corpuscular haemoglobin (MCH) – 26 pg (reference range 27–35 pg)
- red cell distribution width (RDW) – 17% (reference range 12–15%)
- white cell count and platelet count – within reference range
- blood film comment: mild hypochromia.

Iron studies show the following results:

- serum ferritin – 24 µg/L (reference range 15–290 µg/L)
- serum iron – 10 µmol/L (reference range 10–30 µmol/L)
- total iron-binding capacity – 72 µmol/L (reference range 45–70 µmol/L)
- transferrin saturation – 12% (reference range 16–50%).

Other tests:

- CRP – within reference range
- eGFR – within reference range.

QUESTION 3

What is your interpretation of Mary's test results?

QUESTION 4

What are the next steps in Mary's management plan?

FURTHER INFORMATION

Mary commences oral iron treatment but returns two weeks later informing you that she has stopped taking it because of significant gastric upset and constipation. She had called the practice nurse, who suggested taking a lower dose just before bed every second day, but this did not solve the problem.

QUESTION 5

What are the treatment options now?

QUESTION 6

What advice would you give Mary regarding her medication management prior to surgery?

QUESTION 7

What information would you provide regarding possible perioperative blood transfusion?

CASE 2 ANSWERS

ANSWER 1

Box 1 highlights blood management questions when referring a patient for elective surgery.[1]

Box 1. Questions to consider when referring a patient for elective surgery[1]

- What is the extent of likely blood loss?
- Does my patient have anaemia, or are they at risk of anaemia? What are my patient's iron stores?
- Does my patient have comorbidities that may impact on their ability to cope with anaemia? If so, how can these be managed (eg need to assess and optimise cardiac status)?
- Does my patient have any comorbidities that may affect bone marrow response (eg chronic kidney disease, inflammation or bone marrow pathology)?
- What medications or therapies are my patient taking that may increase their risk of bleeding?
- Is my patient informed about the risks/benefits of transfusion and possible options that may reduce or avoid transfusion?

Adapted from: Minck S, Robinson K, Saxon B, Spigiel T, Thomson A. Patient blood management – The GPs guide. Aust Fam Physician 2013;42(5):291–97. Available at www.racgp.org.au/afp/2013/may/patient-blood-management [Accessed 26 November 2015]

Patient blood management (PBM) is a term used to describe the principles of conserving and managing a patient's own blood to improve outcomes.[2] These include:

- identifying and managing anaemia and iron deficiency
- reducing bleeding and blood loss
- working with tolerance of anaemia, thrombocytopaenia and coagulation abnormalities
- ensuring that use of transfusion is in line with best practice.

A total knee replacement surgery places Mary at risk of significant blood loss, so possible preoperative anaemia and suboptimal iron stores should be identified, evaluated and managed.[3] Preoperative anaemia is associated with increased perioperative morbidity and use of transfusion.[3] Patient assessment should occur as early as possible (minimum four weeks, but preferably when the need for surgery is first identified) to allow for optimisation of haemoglobin and iron stores.[3,4] Assessment of iron stores should not be overlooked, as patients with normal haemoglobin levels may have iron stores that are inadequate to respond to significant blood loss.[3]

Where anaemia or iron deficiency is identified, further assessment of the cause, together with its treatment, if possible, is indicated. Depending on the clinical picture, non-urgent surgery may need to be delayed.[3,4]

Where a patient is at an increased risk of anaemia due to comorbidities (eg chronic cardiac or renal disease), specialist preoperative assessment and management planning are essential.

Reducing bleeding during surgery is often considered the surgeon's domain, but general practitioners (GPs) can assist by identifying medications, including complementary therapies, that may increase the risk of bleeding.[1]

An important consideration is Mary's role in her own care. She should be encouraged to ask about the options for her blood management, and be informed of the benefits or risks and how these apply in her own situation.

ANSWER 2

Current Australian guidelines recommend that preoperative full blood evaluation (FBE), iron studies, C-reactive protein (CRP) and renal function be performed as early as possible in patients who are planning to undergo surgery in which substantial blood loss is anticipated.[3] This is to allow investigation and correction if appropriate, and to avoid causing unnecessary delays to surgery.[3,4] Ferritin is an acute phase protein and CRP is recommended to assist in identifying cases where co-existing inflammation may result in misleadingly elevated ferritin levels in iron-deficient patients.[5]

The need for additional investigations, such as B12, folate and liver function tests (LFTs), should be guided by the individual patient's assessment. If the surgery is non-urgent, patients should be counselled about the relationship between anaemia, morbidity and mortality, and be given the opportunity to defer non-urgent surgery until anaemia or iron deficiency is investigated and treated.[4] Useful algorithms for preoperative assessment of anaemia and investigation of causes of iron deficiency are available.[3,5]

ANSWER 3

Although Mary's haemoglobin and ferritin levels are within the reference range for the testing laboratory, she meets the World Health Organization's (WHO's) definition of anaemia (Hb <120 g/L for females and <130 g/L for men)[6] and the Royal College of Pathologists of Australasia's definition of iron deficiency (serum ferritin level of less than 30 µg/L for an adult).[7] She therefore meets the definition of iron deficiency anaemia. Where possible, review of previous FBE results to assess any changes can be very valuable.

'Mild' anaemia is a term often used for haemoglobin just below the cut-off and may indicate a lack of clinical significance; however, any degree of anaemia requires a cause to be determined.

Additional clues to iron deficiency can be found in the FBE. When there is insufficient iron for haemoglobin production, cells become smaller, reflected by a decreasing or decreased MCV, and paler due to reduced haemoglobin, reflected by decreasing or decreased MCH. The variation in size of cells is reflected by an increased RDW.

Ferritin reflects storage iron, and while a low ferritin is the most sensitive and specific marker of iron deficiency, it is also an acute phase reactant, so will be elevated in patients with co-existing infection or inflammation.[5,8,9] In this situation, the transferrin saturation, reflecting transport iron, can be useful. Transferrin saturation levels less than 20% indicate an iron supply that is insufficient to support normal erythropoiesis.[10] This is seen in iron deficiency, but also anaemia of acute or chronic inflammation where iron stores are present but unable to be used due to the action of hepcidin. Total iron-binding capacity increases in iron deficiency in an attempt to increase iron uptake.

As discussed previously, in patients requiring surgery that may result in significant blood loss, the presence of insufficient iron stores means that the ability to replace red cells lost during surgery will be impaired.[3]

ANSWER 4

Mary requires concurrent treatment with iron therapy and investigation of the underlying cause of her iron deficiency. Investigations should not delay treatment. The most common cause of iron deficiency in adults is blood loss.[5]

Mary's age (>75 years), use of non-steroidal anti-inflammatory drugs (NSAIDs) and moderate alcohol intake are possible factors in her iron deficiency; however, a full history and careful clinical examination are necessary. All patients with unexplained iron deficiency or iron deficiency anaemia should be screened for coeliac disease.[5,8,9] Upper and lower gastrointestinal (GI) investigations are recommended for all

Box 2. Oral iron dosing and considerations[11]

- Usual adult dose for iron deficiency anaemia (IDA) is around 100–200 mg elemental iron daily in divided doses
- The dose is ideally given 1 hour before or 2 hours after food
- GI upset may be reduced by taking tablets with food or at night and increasing the dose gradually
- Consider giving supplement with vitamin C (eg orange juice) to improve absorption
- When a rapid increase in haemoglobin is not required, intermittent dosing (one tablet two to three times a week) or lower doses of iron (eg 30–60 mg of elemental iron, increasing to twice daily or three times a day if tolerated: try Ferro-tabs or titrate liquid) may reduce GI upset
- Multivitamin–mineral supplements should not be used to treat IDA as iron content is low and absorption may be reduced
- Iron overdose may be fatal – keep medication out of reach of children
- On the basis of limited available data, controlled-release iron formulations appear to have fewer GI side effects, but similar discontinuation rates and comparable efficacy; release of iron distal to the site of maximal intestinal absorption may theoretically limit response in some patients

National Blood Authority 2015. Iron product choice and dose calculation[11]

males and post-menopausal females with unexplained iron deficiency anaemia.[5,8,9]

Mary requires iron therapy. Increasing dietary iron intake is insufficient to treat iron deficiency, but may be useful for secondary prevention.[5] Oral iron therapy is a suitable and effective first-line therapy for most patients.[5] The recommended daily dose is 100–200 mg of elemental iron in two or three divided doses. Lower dosing or less frequent dosing may be better tolerated and effective in some patients.[5]

It is important to provide specific guidance on iron supplements as there are many over-the-counter preparations that contain insufficient quantities of iron for therapeutic purposes. Information on appropriate iron formulations, together with advice regarding how to take them, and potential side effects and strategies to avoid these, should be provided. Some key points are highlighted in Box 2. Tools to assist with this are available.[11,12,13]

Evaluation of the response to oral therapy should occur after three to four weeks.[3,5] Haemoglobin levels should rise by approximately 20 g/L every three weeks following therapeutic doses of oral iron,[5] provided there is no significant ongoing blood loss and the patient is able to tolerate and absorb therapy.

ANSWER 5

Intramuscular iron is discouraged as it is painful and associated with permanent skin discolouration.[5]

Intravenous (IV) iron is indicated:

- where oral iron is:
  - not tolerated
  - ineffective or response is suboptimal
  - not able to be absorbed
- in situations where rapid replenishment of haemoglobin and iron stores is required (eg more urgent surgery, pre-obstetric delivery).[3,5]

As in Mary's case, where oral iron is poorly tolerated, modification of dose, timing and frequency should, where possible, be trialled prior to considering IV iron.[3,5]

Pharmaceutical Benefits Scheme (PBS) listing of iron carboxymaltose, administered as a single IV dose of up to 1000 mg over 15 minutes, has provided the opportunity for IV iron therapy to be delivered in primary care practice. Dosing and administration guidance and tools are available.[11,12]

ANSWER 6

Mary is at increased risk of bleeding due to her daily intake of non-steroidal anti-inflammatory drugs (NSAIDs) and should be advised that she will need to cease this prior to surgery. Australian guidelines recommend cessation of NSAIDs preoperatively to reduce blood loss, and the timing of cessation should reflect the agent's pharmacology (Grade C recommendation).[3]

Patients on anticoagulant and/or combination antiplatelet therapy will require multidisciplinary assessment to plan management to balance the risk of bleeding and thrombotic events.[3]

Complementary medicines including glucosamine, fish oil products, garlic, ginko biloba and ginseng may have effects on haemostasis. Antiplatelet activity is the most common effect demonstrated in vitro, but other potential actions include interaction with antiplatelet or anticoagulant agents. Discontinuation of complementary medicines before surgery should be considered.[14–16]

It is important that Mary provides an up-to-date medication list at her specialist review and the pre-admission clinic. A plan for the medication management prior to surgery and after discharge should be developed and provided to the patient and GP.

ANSWER 7

Mary is at increased risk of requiring red cell transfusions due to the nature of her surgery, her age and gender, the iron deficiency anaemia and increased risk of bleeding associated with her medications. The blood management strategies discussed so far will assist in reducing that risk. However, she should be advised of the benefits and risks of red cell transfusion and informed of other strategies that may assist in further reducing her need for a transfusion. These include the use of medications such as tranexamic acid during surgery to reduce blood loss, or the use of intraoperative cell salvage.[3] Mary should be encouraged to discuss potential options for blood management with her specialist. Providing a list of questions to ask may help her in this. Choosing Wisely Australia's *5 questions to ask your doctor* is a useful guide (Box 3).[17]

Box 3. Five questions to ask your doctor before you get any test, treatment or procedure[17]

1. Do I really need this test or procedure?
2. What are the risks?
3. Are there simpler, safer options?
4. What happens if I don't do anything?
5. What are the costs?

A competent adult who has been fully informed of the risks and benefits is entitled to make the decision to accept or refuse medical treatment such as blood transfusion. The treating medical team needs to ensure patients have all the information available and all their questions answered to make this decision. The website www.mytransfusion.com.au provides information about transfusion and potential ways to reduce or avoid transfusion.

KEY MESSAGES

- GPs have an important role in their patients' blood management prior to major surgery.
- Preoperative anaemia is common and, as early as possible, should be assessed and managed to improve patient outcomes.
- Preoperative planning to reduce bleeding risk, particularly due to medication effect, is essential to reduce blood loss and risk of transfusion.

- The risks and benefits of transfusion, and potential options to reduce or avoid transfusion, should be discussed as early as possible with any patient for whom transfusion is a possibility.

RESOURCES FOR PATIENTS AND DOCTORS

The following websites provide information and resources about patient blood management, iron deficiency anaemia and blood transfusion for patients:

- www.mytransfusion.com.au
- www.blood.gov.au/fit-surgery-fit-life

RESOURCES FOR DOCTORS

The following websites provide information, education, tools and resources about patient blood management, iron deficiency anaemia and blood transfusion for clinicians:

- www.transfusion.com.au
- www.blood.gov.au
- https://bloodsafelearning.org.au

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CASE 3

TRAN'S CONCERNING BLOOD TESTS

Tran, a local businessman, has been a patient at your practice for 10 years. He migrated from Vietnam in the 1970s and is now aged 62 years. Tran has hypertension and is taking an angiotensin-converting-enzyme (ACE) inhibitor, which is effectively controlling his blood pressure. His last recorded blood pressure (BP) was 125/88 mmHg. He lives with his wife and youngest daughter. He has two other children who live nearby. You see him to follow up on routine blood tests ordered by a colleague two months ago as he has hypertension and scored greater than 50 on the absolute cardiovascular risk (Table 1).

Table 1. Tran's blood tests results

Tests	Results	Reference range
Cholesterol	5.6 mg/dL	–
Triglycerides	4.0 mg/dL	<2 mmol/L
Glycated haemoglobin (HbA1c)	5.5%	(4.0–6.0)%
Full blood evaluation: • Platelets • All others	 130 X 10^9/L Normal	 150–400 10^9/L
Bilirubin	17 µmol/L	<15 µmol/L
Alanine aminotransferase (ALT)	48 U/L	0–30 U/L*
Aspartate aminotransaminase (AST)	85 U/L	<35 U/L
Alkaline phosphatase (ALP)	75 U/L	30–115U/L
Gamma-glutamyl transferase (GGT)	66 U/L	10–50 U/L
Protein	71 g/L	60–85 g/L
Albumin	35 g/L	35–48 g/L

*Note, while some laboratories report normal ALT as up to 56 as accepted, normal levels for men are <30 and women <20.[1]

QUESTION 1

What further information would you need to know on history and physical examination for a further assessment of Tran's liver?

FURTHER INFORMATION

Tran smokes occasionally when he is out with friends, and drinks three to four standard drinks each night of the weekend. In the past, he was a heavier drinker but cut back when he turned 50. Tran is not sure whether or not he has been tested for viral hepatitis in the past, but one of his uncles in Vietnam had liver problems and developed liver cancer at the age of 50 years. Tran has no other family history. He feels well and is surprised by the abnormal tests, which suggest he might have something wrong with his liver.

On examination, his BMI is 28 kg/m^2, waist circumference is 98 cm and there are three spider naevi on his upper chest.

QUESTION 2

On the basis of Tran's blood test results, history and physical examination, what is the suspected diagnosis? What are the three most likely causes?

QUESTION 3

What further tests would you order to determine the cause of Tran's abnormal liver tests?

FURTHER INFORMATION

You order the additional tests for hepatitis B and C, and a liver ultrasound to determine the cause of his abnormal liver tests. The results are shown in Box 1.

Box 1. Tran's further tests

- HBsAg: positive
- Anti-HBc: positive
- Anti-HBs: negative
- Hepatitis C virus antibody: negative
- Liver ultrasound: mild fatty liver, otherwise normal and normal portal flow

QUESTION 4

Given Tran's tests results in Box 1, what would be your diagnosis?

QUESTION 5

What further testing is required to determine the phase of CHB?

QUESTION 6

What other blood tests should you consider in Tran's initial assessment? What is your reason for the tests?

FURTHER INFORMATION

Tran's viral load is 1750 IU/mL. He is positive for anti-HBe and hepatitis A virus immunoglobulin G (HAV-IgG).

QUESTION 7

What phase of CHB is Tran in? What further management is required?

FURTHER INFORMATION

You refer Tran to the local liver clinic, which organises a FibroScan test. His reading is 17 kPa, indicating that he is likely to have cirrhosis (cirrhosis >12.5 kPa). He is commenced on entecavir 0.5 mg daily. Tran has a gastroscopy to screen for oesophageal varices, which is negative. He is returned to your care.

QUESTION 8

What further management is required for a patient with chronic hepatitis B and cirrhosis?

CASE 3 ANSWERS

ANSWER 1

From Tran's test results (Table 1), you conclude that he may have a liver disease. You would need to know more about his history:

- alcohol and smoking history
- family history of liver disease or liver cancer
- previous history of illness
- previous screening for viral hepatitis or risk factors for viral hepatitis
- body mass index (BMI)
- signs of chronic liver disease
  - spider naevi
  - hepatic palms (palmar erythema)
  - nail changes (leukonychia)
  - gynaecomastia
  - hepatosplenomegaly
- signs of portal hypertension
  - collateral vessels on anterior abdominal wall
  - caput medusa (venous structures around the umbilicus)
  - ascites
  - varices.

ANSWER 2

Given Tran's test results, further history and physical examination, the most likely diagnoses are chronic liver disease or cirrhosis. He has low platelets, a reversal of AST:ALT ratio and clinical signs suggestive of liver disease.

The three most likely causes of chronic liver disease and cirrhosis are:

- alcohol consumption – he has a history of excessive consumption
- chronic viral hepatitis – people born in Vietnam have an 8–10% chance of having chronic hepatitis B (CHB); he also has a family member with liver cancer
- fatty liver – he is overweight.

ANSWER 3

To determine the cause of Tran's abnormal liver tests, you would need to order further tests with informed consent:

- hepatitis B serology
  - hepatitis B surface antigen (HBsAg)
  - hepatitis B core antibody (anti-HBc)
  - hepatitis B surface antibody (anti-HBs)
- hepatitis C virus antibody
- ultrasonography of the liver, including portal Doppler.

ANSWER 4

Tran's test results indicate a diagnosis of CHB infection, fatty liver and suspected cirrhosis. In an individual born in a high prevalence country, the diagnosis of CHB is most likely to represent chronic infection in the setting of no recent exposure or illness:

- HBsAg: positive indicates current infection with the HBV virus
- Anti-HBc: positive in both chronic infection and resolved infection
- Anti-HBs: negative in chronic infection and positive in either vaccine-induced immunity or past resolved infection.

If an acute infection is suspected, it can be confirmed by an IgM anti-HBc. In Australia, most people living with CHB are born overseas, and the prevalence of the infection in communities here is broadly the same as in their country of origin. CHB infection results in significant disease-related mortality in 15–25% of people living with the infection. It is a cause of liver cancer, which is the fastest increasing incident cancer in Australia.

ANSWER 5

CHB is a chronic viral infection that requires ongoing management and monitoring. The phases of CHB are related to viral load and damage to the liver. Current recommendations are that everyone with an infection should have a baseline assessment and then at least yearly blood tests, including assessment of viral load.

Therefore, testing to determine the phase of Tran's CHB would include:

- hepatitis B virus DNA (viral load)
- hepatitis B e-antigen (HBeAg) and hepatitis B e-antibody (anti-HBe).

ANSWER 6

Further blood tests for Tran include:

- hepatitis A serology to see if he needs to be offered vaccination
- hepatitis D (HDV) serology
- human immunodeficiency virus (HIV) testing for co-infection (co-infection with HIV or HCV is associated with worse outcomes and faster progression of liver disease)
- prothrombin time (PT), if not previously ordered for synthetic liver function
- ferritin, ceruloplasmin and alpha-1 antitrypsin to check for other causes of liver disease
- alpha-fetoprotein (AFP) as part of surveillance for hepatocellular carcinoma.

ANSWER 7

Tran's results indicate that he has phase 3 CHB (Figure 1), but the previous tests also indicate that he might have cirrhosis. Therefore, Tran should be referred to a specialist for further assessment of his liver disease[1] and consideration of antiviral treatment. Current guidelines recommend that all people with CHB and cirrhosis require evaluation in a specialist service. Antiviral treatment for

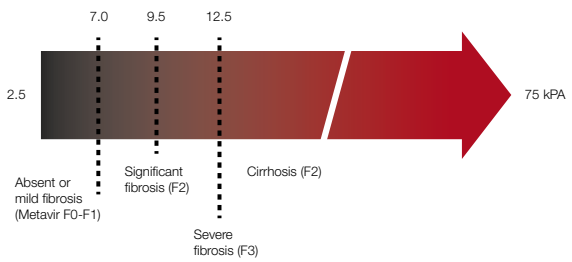
CHB is recommended for patients in phases 2 and 4 of the infection **and** all patients with cirrhosis regardless of what phase they are in. Treatment prevents further liver damage, can reverse cirrhosis and reduces the risk of liver cancer. Oral treatments are well tolerated but usually considered as long-term therapy.[2]

Transient elastography, most commonly FibroScan, is a quick, non-invasive test to check the stiffness of the liver. This test is available in most liver clinics and has reduced the need for liver biopsy. It is a useful tool to exclude cirrhosis, and a reading >12.5 kPa is suggestive of cirrhosis (sensitivity 85% and specificity 82%).[3] A BMI >35 and liver inflammation (high ALT) can return false positive results. Some tertiary centres provide a FibroScan service that can be used prior to referral and allow for prioritisation of people with cirrhosis.

All of Tran's family should also be tested for CHB and vaccinated if susceptible.[4]

Tran should also undergo hepatocellular carcinoma surveillance with ultrasonography every six months as he is of Asian descent, has cirrhosis and is older than 40 years of age.[5]

Figure 1. FibroScan suggested cut-off



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ANSWER 8

Management for patients with chronic hepatitis B and cirrhosis includes:

- hepatocellular carcinoma surveillance six monthly (all patients with cirrhosis)
- medication monitoring to check for adherence to antivirals at each visit
- appropriate vaccinations (eg hepatitis A unless already immune, seasonal influenza, pneumococcus)
- lifestyle modification advice: maximise health through smoking cessation and reduction of alcohol consumption
- weight loss advice to improve his fatty liver (consider treatment of high triglycerides if no improvement in fatty liver).[1,2]

RESOURCES FOR PATIENTS

- Hepatitis Australia, www.hepatitisaustralia.com

RESOURCES FOR DOCTORS

- Further information regarding testing for the hepatitis B virus, http://testingportal.ashm.org.au
- A two-page decision-making guide,www.ashm.org.au/Documents/HBV_DecisionMaking_Jan15.pdf
- Detailed resource on management of chronic hepatitis B, http://hepatitisb.org.au
- HepBHelp is an independent website that aims to assist GPs in the further investigation and management of patients diagnosed with CHB, www.hepbhelp.org.au

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CASE 4

BILL PRESENTS WITH HEADACHES AND FATIGUE

Bill, a policeman aged 43 years, presents with a history of headaches and fatigue. You order a full blood evaluation (FBE), including iron studies. This reveals Bill's ferritin levels are 1362 µg/L, which exceeds the normal range of 30–500 µg/L (Table 1).

Table 1. Results of Bill's blood test

Test	Result	Normal value
Haemoglobin	164 g/L	130–180 g/L
Haematocrit	0.47	0.40–0.54
MCV	89 fL	80–100 fL
Platelets	142 x 10^9	150–400 x 10^9
White cell count	4.6 x 10^9	4.0–11.0
Sodium	141 mmol/L	135–145 mmol/L
Potassium	3.7 mmol/L	3.5–5.5 mmol/L
Urea	5.0 mmol/L	3.0–8.0 mmol/L
Creatinine	83 µmol/L	60–110 µmol/L
eGFR	88	>60
Total bilirubin	11 µmol/L	4–20 µmol/L
ALT	57 U/L	5–40 U/L
AST	28 U/L	10–40 U/L
ALP	61 U/L	35–110 U/L
GGT	32 U/L	5–50 U/L
Protein	68 g/L	66–83 g/L
Albumin	41 g/L	37–48 g/L
C-reactive protein	5 mg/L	<5 mg/L
Fasting BGL	5.2 mmol/L	<5.5 mmol/L
Cholesterol	4.3 mmol/L	<5.5 mmol/L
Triglyceride	1.0 mmol/L	<1.8 mmol/L
HDL cholesterol	0.9 mmol/L	1.1–3.5 mmol/L
LDL cholesterol	2.9 mmol/L	<3.5 mmol/L
TSH	1.62 mU/L	0.5–5.0 mU/L
B12	465 pmol/L	139–651 pmol/L
Fasting ferritin	1384 µg/L	30–500 µg/L
Transferrin	24 µmol/L	25–40 µmol/L
Transferrin saturation	79%	10–45%
Iron	38 µmol/L	5–30 µmol/L

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; GGT, gamma glutamyl transferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MCV, mean corpuscular volume; TSH, thyroid stimulating hormone

QUESTION 1

What are the important findings on history taking and physical examination that will help identify the underlying cause and clinical significance of hyperferritinaemia?

FURTHER INFORMATION

Bill's only symptoms are headaches and fatigue. There are no indications of a recent infection. He has no reported arthralgia, loss of libido, polyuria or cardiac symptoms. Bill has no significant past medical history, including diabetes mellitus, liver disease, cardiac disease and arthritis. He does not take any medications. Bill drinks on average three standard drinks per day and is an ex-smoker. He was adopted and therefore does not know his family history.

On examination, Bill weighs 100 kg and has a body mass index (BMI) of 29 kg/m^2. He has no evidence of skin pigmentation, arthropathy, signs of chronic liver disease or hepatosplenomegaly. His heart sounds were dual with no murmurs, cardiomegaly or signs of congestive heart failure.

QUESTION 2

What are the differential diagnoses for hyperferritinaemia? What additional tests would you order to help determine the cause of Bill's hyperferritinaemia?

FURTHER INFORMATION

Hepatitis B surface antigen and hepatitis C antibodies are not detected in Bill's blood tests. Testing for the haemochromatosis gene detects a C282Y homozygous mutation but no H63D mutation (which would not be possible in the presence of a homozygous C282Y mutation). The liver ultrasound shows no evidence of steatosis or cirrhosis.

QUESTION 3

What do the additional test results indicate? What is the biochemical and clinical penetrance of the C282Y mutation?

QUESTION 4

What is the mechanism for iron overload in *HFE*-related haemochromatosis?

QUESTION 5

What are the disease manifestations of iron overload?

QUESTION 6

With the knowledge that C282Y homozygous mutations have variable penetrance, how do we assess iron overload?

FURTHER INFORMATION

Bill was referred to a hepatologist for ongoing investigation and management. A FerriScan was ordered to quantify his iron overload. His average liver-iron concentration measured 225 mmol/kg dry tissue (normal range 3–33 mmol/kg). This is seven times the upper limit of normal. The positive predictive value of this test for identifying iron overload likely to cause iron-induced complications is 87%.[1]

QUESTION 7

What non-invasive methods are used to assess the level of fibrosis in HH?

FURTHER INFORMATION

Bill's ferritin is higher than 1000 µg/L (30–500 µg/L), which gives him an estimated 36% chance of having cirrhosis.[2] He went on to have a FibroScan with a liver stiffness measurement of 5.2k Pa. This has a 100% negative predictive value for cirrhosis, eliminating the need for a liver biopsy.[3] Had his Fibroscan been between 6.4 and 13.9 kPa, a liver biopsy may have been required to accurately quantify the fibrosis level.

QUESTION 8

In patients with C282Y HH, when should phlebotomy be initiated?

FURTHER INFORMATION

Bill was referred for weekly venesection at the Australian Red Cross Blood Service. After 20 venesections, his ferritin fell from 1384 µg/L to 362 µg/L. After another six venesections (total 26 equivalent to 6.5 g iron), Bill's ferritin had reached 72 µg/L and he was commenced on a maintenance three-month phlebotomy program.

QUESTION 9

What clinical features have been shown to improve with venesection?

QUESTION 10

What is the expected survival of patients with HH? Which family members should be screened for HH?

CASE 4 ANSWERS

ANSWER 1

The purpose of the history and physical examination is to identify a cause for the hyperferritinaemia and to search for clinical manifestations of iron overload. The history should be thorough and include a systemic enquiry, past medical history, family history and drug and alcohol history.

The systemic enquiry should include questions aimed at identifying an inflammatory, infective or neoplastic cause of hyperferritinaemia. Constitutional symptoms such as weight loss, night sweats and fever are less suggestive of hereditary haemochromatosis (HH), and may suggest one of the above disease processes. Factors that increase the likelihood of HH include Northern European ancestry or a positive family history of HH. Conversely, an elevation of ferritin in non-Caucasian populations is likely to be attributed to a secondary or non-HFE-related cause.[4]

Secondary causes of hyperferritinaemia and iron overload are common and include viral hepatitis, alcoholic liver disease and non-alcoholic steatohepatitis. Patients at risk can be identified by their heavy alcohol consumption, past history of intravenous drug use or metabolic syndrome. Symptoms related to iron overload include fatigue, arthralgia (arthropathy), loss of libido (hypogonadism), thirst and polyuria (diabetes), orthopnea (congestive cardiac failure), ascites and encephalopathy (liver cirrhosis).

Physical examination can also identify complications relating to iron overload. Skin pigmentation may be seen in some patients with HH. Hepatomegaly is uncommon at presentation, but when present, the liver feels firm and regular. Cirrhosis is a late and uncommon complication of HH. However, identifying clinical signs associated with liver cirrhosis (palmar erythema, spider naevi, gynaecomastia and ascites) is important because of the clinical consequences. Hypogonadism occurs due to iron deposition in the pituitary gland and can also be a consequence of chronic liver disease. Patients with hypogonadism may have gynaecomastia and a decrease in body hair. The arthropathy associated with HH is a symmetrical small-joint arthropathy that affects the metacarpophalangeal and proximal interphalangeal joints. It presents in a similar way to rheumatoid arthritis; however, arthralgia is more frequent than synovitis.[5]

ANSWER 2

Differential diagnoses for hyperferritinaemia include:

- acute inflammation (eg infection)
- chronic inflammation (eg systemic lupus erythematosus)
- malignancy
- haemophagocytic lymphohistiocytosis
- hereditary hyperferritinaemia-cataract syndrome
- iron overload syndromes

- hereditary haemochromatosis (HH)
  - Type 1 – *HFE*-related (eg C282Y/C282Y, C282Y/H63D and other *HFE* mutations)
  - Type 2 – juvenile haemochromatosis (eg haemojuvelin [HJV], hepcidin [HAMP])
  - Type 3 – transferrin receptor-2 (TfR2)
  - Type 4 – ferroportin (SLC40A1; eg loss of function, gain of function)
- secondary iron overload
  - iron-loading anaemias (eg thalassaemia major, sideroblastic, chronic haemolytic anaemia, aplastic anaemia)
  - parenteral iron overload (eg red blood cell transfusions, iron-dextran infusions, long-term haemodialysis)
  - chronic liver disease (eg porphyria cutanea tarda, hepatitis B, hepatitis C, alcoholic liver disease, non-alcoholic liver disease, following portocaval shunt)
- miscellaneous
  - congenital alloimmune hepatitis (neonatal iron overload)
  - African iron overload
  - aceruloplasminaemia
  - congenital atransferrinaemia.[6]

Bill should have tests for hepatitis B and C and mutations in the haemochromatosis gene (*HFE*). He should also have a liver ultrasound. A Medicare rebate for *HFE* testing would apply if Bill had elevated transferrin saturation or ferritin on repeated testing.

ANSWER 3

The presence of a C282Y homozygous mutation indicates a diagnosis of *HFE*-related HH.[6] Bill does not have additional risk factors for iron overload. Specifically, he does not have viral hepatitis, excessive alcohol use or metabolic syndrome. His C-reactive protein (CRP) is normal, which helps to exclude infection or an inflammatory condition as a potential cause of hyperferritinaemia.

The C282Y allele, the *HFE* allele most commonly associated with haemochromatosis, has a frequency of 6.2% in the general population. Homozygosity for C282Y has a prevalence of 1 in 190 (0.5%) and accounts for 80–85% of patients with HH.[6] It is important to note that only 70% of patients with C282Y homozygosity will have serum ferritin levels above the upper limit of normal.[8,9] Even fewer patients will progress to having disease related to iron overload (28% of men and 1% of women), liver fibrosis (14%) and cirrhosis (3%).[8] The reason for the variable penetrance is likely to be a combination of environmental and genetic factors. Environmental factors such as blood loss in women, diet and the presence of other liver disease processes (eg alcohol, non-alcoholic steatohepatitis) can contribute to the development of iron overload–related disease.[6] Various genetic modifiers have been identified as influencing the clinical expression of HFE-related haemochromatosis and may serve as predictors of phenotype in the future.[6]

ANSWER 4

The C282Y mutation results in abnormal hepcidin expression, which is responsible for uncontrolled iron absorption from the gut and iron release from reticuloendothelial cells as a result of unhindered export by ferroportin, leading to visceral iron overload in some patients. Iron accumulates preferentially in hepatocytes. It is hypothesised that iron causes the production of oxyradicals and the peroxidation of lipid membrane that leads to organelle damage and cellular necrosis. Production of cytokines and growth factors activates hepatic stellate cells, which are a source of collagen and fibrosis.[6]

ANSWER 5

Prognosis of HH is directly related to the stage of liver fibrosis. Therefore, in patients at risk, such as those with ferritin >1000 µg/L (reference range 30–500 µg/L),[10] the fibrosis level needs to be assessed to guide ongoing management. A diagnosis of cirrhosis has important implications and would prompt regular screening for complications of liver cirrhosis, including oesophageal varices and hepatocellular carcinoma (HCC). Patients with haemochromatosis and cirrhosis have a greater than 100-fold chance of developing HCC, compared with the general population.[11]

Extrahepatic clinical manifestations include fatigue, diabetes mellitus, skin pigmentation, arthritis, cardiomyopathy, hypothyroidism, osteoporosis and hypogonadism.[12]

ANSWER 6

Serum ferritin

- Highly sensitive test for iron overload in haemochromatosis. Normal serum ferritin concentration excludes iron overload.[9]
- Serum iron and transferrin saturation do not quantitatively reflect body iron stores and should not be used as a surrogate marker of tissue iron overload.[13]

Amount of iron removed

- The total number of phlebotomies required to achieve low normal range concentrations of serum ferritin may be a useful retrospective surrogate marker for iron overload.
- One unit of blood equals 250 mg of iron. Removal of 5 g or more of iron (20 weekly venesections) without developing iron deficiency anaemia indicates iron overload.[14]

Liver biopsy

- The measurement of liver iron concentration (LIC) is clinically useful because LIC reflects total body iron in a predictable way.
- Liver biopsy, the so-called gold standard for LIC determination, is highly variable. Single LIC measurements can be very imprecise in livers with moderately high mean LIC and decrease as the overall load of the liver increases. Accuracy is also limited by the pathologists' experience, the size of the sample and the presence of cirrhosis.[15]
- The advantage of a liver biopsy is that it provides additional valuable information about other potential causes of deranged liver function and liver pathology.

- It is important to recognise that morbidity and mortality can be associated with liver biopsy. Bleeding risk can occur in up to 3.6% of cases, with an associated mortality rate of one in 10000.[16,17]

Magnetic resonance imaging

- Magnetic resonance imaging (MRI) is available in Australia and is of proven accuracy in the rapid, non-invasive measurement of LIC. This test is not on the Medicare Benefits Schedule (MBS) but any clinician can refer patients to MRI facilities that offer this measurement.
- As indicated above, liver biopsy has significant risks and limitations. Therefore, the ability to measure LIC non-invasively is an important component to managing iron storage disorders.
- MRI techniques available in Australia are based on measurement and imaging of proton transverse relaxation rates (R2) within the liver (FerriScan).[1]
- A recent meta-analysis of 20 MRI studies with 819 patients investigated the diagnostic accuracy of MRI in identifying iron overload. The analysis was limited by the substantial heterogeneity between studies and highly variable diagnostic accuracy. The median sensitivity and specificity was 0.94 and 0.92 respectively. FerriScan had a sensitivity of 0.90 (0.85–0.94) and specificity of 0.87 (0.76–0.93) for identifying patients with an LIC of >7 mg/g dry liver weight, which is the threshold associated with iron-induced complications.[3]

The presence of hyperferritinaemia and the homozygous C282Y genotype in the absence of inflammation, infection, metabolic syndrome or alcohol abuse is sufficient to confirm iron overload. In practice, many patients have multiple risk factors for hyperferritinaemia and either MRI or the amount of iron removed is required to confirm iron overload. The choice of technique will depend on local expertise, cost and availability. Biopsy is now reserved for the evaluation of patients with suspected co-existing liver disease such as non-alcoholic steatohepatitis.

ANSWER 7

FibroScan

- Transient elastography is a non-invasive method used to assess liver fibrosis. It is based on the measurement of the velocity of propagation shear wave through the liver. Velocity, expressed as kilopascals (kPa), is correlated with the amount of fibrosis in the liver.
- FibroScan is used as a tool in predicting liver fibrosis in hepatitis C, and the European Association for the Study of the Liver (EASL) recommends its use.
- A recent study by Legros[18] of 77 patients with confirmed C282Y HH examined the diagnostic performance of FibroScan to predict liver fibrosis, referenced to liver biopsy. All patients had a ferritin >1000 and elevated ALT. The range of fibrosis levels in the patient group were F0 in 14.3%, F1 in 42.9%, F3 in 2.5%, F4 in 16.9% (19.5% had F3–4, which is indicative of severe fibrosis). The study found that a FibroScan cut-off of 6.4 kPa and 13.9 kPa gave a 100% negative predictive value and positive predictive value respectively for severe fibrosis. Therefore, patients who have a FibroScan level <6.4 kPa or >13.9 kPa can avoid the need for a liver biopsy.
- FibroScan requires referral to either a private hepatologist or a public outpatient hepatology service. This test is not on the MBS.

Hyaluronic acid

- Hyaluronic acid is significantly increased in HH patients with cirrhosis when compared to those without. A cut-off value of 46.5 provided an area under the curve of 1.0 (100% sensitivity and specificity) for predicting cirrhosis.[19]
- It is not recommended in the guidelines nor available for routine testing in Australia.

Hepascore

- Hepascore is a serum marker of fibrosis that has not been validated in HH.
- Hepascore is available in Australia but not on the MBS. GPs are able to request this test.

Clinical signs, imaging and biochemistry can help diagnose cirrhosis in all types of liver disease. If none of these parameters indicate underlying cirrhosis, then Fibroscan is useful in testing for the presence or absence of cirrhosis. This test is commercially available in Australia and, as indicated above, small studies have validated its accuracy in HH patients.

ANSWER 8

If ferritin is not elevated and the patient is homozygous for C282Y, then the patient should have once-yearly iron studies.[20] The American Association for the Study of Liver Diseases (AASLD) recommends treating HH when ferritin levels are above the upper limit of normal.[12] The benefit of phlebotomy on survival has been shown in large, retrospective cohort studies in patients with and without cirrhosis.[21,22]

However, there are no studies providing data to direct the optimal time or ferritin level at which to start venesection. This question is the subject of a current randomised controlled trial,[23] but until the data is available, all patients with C282Y HH and elevated ferritin with symptoms and evidence of iron overload should continue to be venesected with the aim of achieving a ferritin of 50–100 µg/L.

The Australian Red Cross Blood Service High Ferritin application will provide a recommended schedule of phlebotomy once the ferritin is entered for subjects with HH.[24] Once patients are in the maintenance phase, haemoglobin should be monitored at each venesection and should be postponed if anaemia is detected.

ANSWER 9

Clinical features to be ameliorated by phlebotomy include malaise, skin pigmentation, insulin requirements for patients with diabetes, and portal hypertension. Clinical features that may also respond but to a lesser extent include arthropathy, hypogonadism and advanced fibrosis.[20]

ANSWER 10

Survival is reduced in patients with C282Y HH complicated by cirrhosis or diabetes mellitus.[21,22] The main cause of death is hepatic decompensation (32%) and HCC (23.1%).[22] By contrast, patients

without cirrhosis and diabetes had similar expected survival to those without C282Y HH.[21,22] Therefore, patients diagnosed and treated in the pre-cirrhotic and pre-diabetic phase should have a life expectancy equivalent to the general population.

Once a patient with C282Y HH has been identified, family screening should be recommended for all first-degree relatives. For ease of testing, both genotype and phenotype (ferritin and transferrin saturation) should be performed simultaneously.

Prior to testing a patient's child, it is recommended that the proband's partner is tested and if no C282Y mutation is detected then there is no need to test children.[12] It is not recommended that individuals under the age of 18 years are routinely tested.

RESOURCES FOR DOCTORS

- Bacon BR, Adams PC, Kowdley KV, Powell LW, Tavill AS, American Association for the Study of Liver Diseases. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology 2011;54(1):328–43. Available at www.aasld.org/sites/default/files/guideline_documents/Hemochromatosis2011.pdf
- Australian Red Cross Blood Service High ferritin app, https://highferritin.transfusion.com.au
- Elevated serum ferritin: What should GPs know, www.racgp.org.au/afp/2012/december/elevated-serum-ferritin
- Haemochromatosis Australia, list of resources for GPs, http://haemochromatosis.org.au/gpresources

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CASE 5

JUNE HAS AN IRREGULAR PULSE

June, 75 years of age, comes to see you about her irregular pulse. She has also frequently had palpitations, weakness, decreased effort tolerance and dyspnoea.

QUESTION 1

What are the common causes of an irregular pulse? How would you initially assess June?

FURTHER INFORMATION

June's medical history includes hypertension and type 2 diabetes. She had a stroke two years ago without any residual weakness. She has no history of heart failure, ischaemic heart disease or peripheral arterial disease.

June's medications include perindopril 10 mg daily, aspirin 100 mg daily and metformin 500 mg twice daily. Her electrocardiogram (ECG) confirms atrial fibrillation (AF) with a ventricular rate of 87 beats per minute. Her thyroid function and renal/liver function tests were normal.

QUESTION 2

What is the treatment strategy for AF? What are the risks associated with AF? What are the common agents used to control heart rate/rhythm in AF?

QUESTION 3

How would you assess June's risk of thromboembolism?

QUESTION 4

Which anticoagulation agent would you recommend, if any? What are the factors that need to be considered before starting new oral anticoagulants (NOACs)?

QUESTION 5

Can antiplatelet agents, such as aspirin or clopidogrel, be used as an alternative to an anticoagulant?

QUESTION 6

What is June's bleeding risk? What is the role of anticoagulation in valvular AF?

FURTHER INFORMATION

June was referred to a cardiologist who ordered an echocardiography, which was normal. She remains stable on rivaroxaban without any complications. Given she has a HAS-BLED score of 3, June was advised to seek medical advice for any form of bleeding. She was also reviewed in the surgery on a regular basis to monitor bleeding.

However, one year later, June developed a non-melanomatous skin lesion. Biopsy was recommended to evaluate this further.

QUESTION 7

Does June need to stop rivaroxaban prior to the procedure? If so, how soon before should this cease?

QUESTION 8

If temporary cessation of anticoagulant therapy with NOAC is required, would bridging treatment be necessary?

QUESTION 9

If anticoagulant therapy is ceased prior to a procedure, when would you consider restarting it after the procedure?

FURTHER INFORMATION

June presents a few months later with symptoms of upper gastrointestinal bleeding. She was referred to her local hospital emergency department for urgent evaluation and management.

QUESTION 10

How would June's bleeding be managed?

CASE 5 ANSWERS

ANSWER 1

AF typically causes an irregularly irregular pulse. However, a number of other clinical conditions can also cause an irregular (either regularly irregular or irregularly irregular) pulse, including:

- second-degree heart block
- atrial or ventricular ectopic
- atrial flutter with variable heart block
- sinus arrhythmia (generally causes regularly irregular pulse).

Some of the conditions are relatively benign, whereas other conditions are not. An ECG is very important in order to establish the diagnosis. In AF, there is typically an absence of P waves, and irregularly irregular QRS complexes.[1]

A full medical history and physical examination should be performed to exclude signs of structural heart disease and/or heart failure. A bedside ECG should establish the diagnosis. Basic blood tests, including thyroid function test, and an echocardiography should be performed to try to determine the underlying cause of June's AF.

ANSWER 2

The treatment strategy for AF involves:[2]

- control of ventricular rate using pharmacological agents
- achievement and maintenance of sinus rhythm (rhythm control) by pharmacological means or cardioversion in symptomatic individuals
- minimising the risk of thromboembolism with anticoagulant agents
- treatment of the underlying condition.

The major risk associated with AF is thromboembolism, including stroke. Factors that predispose to stroke include increasing age, history of previous stroke or transient ischaemic attack (TIA), hypertension, diabetes, congestive cardiac failure and current smoking. Other factors also include female sex and vascular disease.[3]

Pharmacological agents commonly used to control ventricular rates in AF are beta blockers (eg metoprolol, atenolol), non-dihydropyridine calcium channel blockers (eg diltiazem, verapamil) or digoxin. Intravenous amiodarone can be useful for rate control in selected patients. Atrioventricular (AV) nodal ablation with permanent ventricular pacing is reasonable to control heart rate when pharmacological therapy is inadequate, the patient experiences unacceptable side effects to medications or when rhythm control is not achievable.

Drugs commonly used for termination of atrial fibrillation and maintenance of sinus rhythm (rhythm control strategy) are flecanide, amiodarone and sotalol.

ANSWER 3

There are different stroke risk stratification schemes to optimise antithrombotic/anticoagulant treatment. For patients with non-valvular AF,[4,5] the $CHADS_2$ score is a commonly used, validated, clinical prediction score that uses congestive heart failure, hypertension, age >75 years, diabetes and history of stroke or TIA in a cumulative manner to estimate expected stroke rate per 100 patient years (Table 1).[4,5] Unfortunately, the $CHADS_2$ score has limitations and does not include many common potential stroke risk factors such as female sex and left ventricular ejection fraction.

Instead, new guidelines developed by the European Society of Cardiology[6] recommend a risk factor–based approach with a new schema, the CHA_2DS_2-VASc score (Table 1). The CHA_2DS_2-VASc schema places greater emphasis on major risk factors, including age >75 years and previous episodes of stroke/TIA, by allocating two points to each, with one point for the presence of each of the other clinically relevant non-major risk factors. The CHA_2DS_2-VASc score improves risk prediction and is better at identifying 'truly low-risk' patients with AF. Table 2 shows the adjusted risk of stroke for $CHADS_2$ and CHA_2DS_2-VASc scores. In patients with CHA_2DS_2-VASc score ≥2, anticoagulation has net clinical benefit.

Table 1. Risk assessment of non-valvular AF[4–6]

$CHADS_2$	Score	CHA_2DS_2-VASc	Score
C: congestive heart failure	1	**C**: congestive heart failure	1
H: hypertension	1	**H**: hypertension	1
A: age ≥75 years	1	**A_2**: age ≥75 years	2
D: diabetes	1	**D**: diabetes	1
S_2: stroke history	2	**S_2**: stroke history	2
		V: vascular disease	1
		A: age 65–74 years	1
		Sc: sex category female	1

Table 2. Adjusted risk of stroke for $CHADS_2$ and CHA_2DS_2-VASc scores[4–6]

Score	$CHADS_2$ (% per year)	CHA_2DS_2-VASc (% per year)
0	1.9	0
1	2.8	1.3
2	4.0	2.2
3	5.9	3.2
4	8.5	4.0
5	12.5	6.7
6	18.2	9.8
7		9.6
8		6.7
9		15.2

June's CHA_2DS_2-VASc score can be calculated as follows:

- Age 75 years: 2 points*
- Stroke history: 2 points
- Hypertension: 1 point
- Diabetes mellitus: 1 point
- Female sex: 1 point

*$CHADS_2$ assigns 1 point for age ≥75 years.

June's CHA_2DS_2-VASc score is 7, which places her at high risk of a stroke and, on that basis, anticoagulant therapy is recommended. A beta-blocker such as metoprolol 25 mg twice daily can be used to control her ventricular rate. Her aspirin should be ceased.

ANSWER 4

Oral anticoagulation in the form of a vitamin K antagonist (VKAs), such as warfarin, is a well-established treatment for stroke prevention in patients with AF. VKAs are also used extensively in the treatment and prevention of deep vein thrombosis, pulmonary embolism and for prevention of thromboembolism in mechanical valve.[2,7]

NOACs have recently emerged as an alternative for VKAs and are now widely available. They are currently indicated for:[7]

- prevention of stroke in patients with non-valvular AF with moderate-to-high risk of thromboembolism according to CHA_2DS_2VASc/$CHADS_2$ score
- prophylaxis of deep vein thrombosis/pulmonary embolism in patients undergoing knee or hip replacement surgery
- treatment of deep vein thrombosis/pulmonary embolism.

There is insufficient evidence to recommend one NOAC over another, although some patient characteristics, drug compliance and tolerability, drug interaction and cost may be important considerations in the choice of agent.[6] Though there is a lack of head-to-head trials, debigatran 110 mg BD and apixaban seems to have a slightly lower bleeding risk profile. June was prescribed with rivaroxaban 20 mg once daily due to her preference of once-daily dosage.

The major positive aspects of NOACs over VKAs are that:[8]

- they do not require regular international normalised ratio (INR) monitoring
- there is a reduced risk of adverse interactions with concomitant use of other drugs or changes in diet
- they have been proven to be effective for prevention of strokes
- effective antidotes have recently become available.

Important landmark trials have shown all NOACs to be at least non-inferior to VKAs, with less major bleeding risk in patients with non-valvular AF.

In the Rocket AF trial,[9] rivaroxaban was non-inferior to warfarin for the prevention of stroke and thromboembolism. This trial enrolled 14,264 patients who were randomised to either rivaroxaban or warfarin. The risk of major bleeding in the rivaroxaban group was no different when compared with the warfarin group, while intracranial haemorrhage (0.5% versus 0.7%, $P = 0.02$) and fatal bleeding (0.2% versus 0.5%, $P = 0.003$) were reduced.

Apixaban was evaluated against warfarin in the ARISTOTLE trial[10] in which 18,201 patients were enrolled. Apixaban was superior to warfarin in preventing stroke or systemic embolisation, while causing less bleeding and mortality.

Dabigatran was compared with warfarin in the RELY trial[11] in which 18,113 patients were enrolled. Dabigatran at a dose of 110 mg was associated with rates of stroke and systemic embolism that were similar to those associated with warfarin (1.53% versus 1.69%, $P < 0.001$), as well as lower rates of major haemorrhage (2.71% per year in the group receiving 110 mg dabigatran as compared with 3.36% per year in the group receiving warfarin; $P = 0.003$).

Also, a recent meta-analysis[12] found that NOACs, including direct thrombin inhibitors and Factor Xa inhibitors, are superior to VKAs in terms of residual thromboembolic risk post-anticoagulation in patients with mild-to-moderate renal function (estimated glomerular filtration rate [eGFR] >30 ml/mins). They also have better safety profiles with less risk of major bleeding.

Factors that need to be considered before starting an NOAC include the following.

Renal function

Before starting NOACs, one of the most important considerations should be renal function. Most of the NOACs are contraindicated if there is significant renal impairment (eGFR <30 ml/min). If there is moderate renal impairment, NOACs should be used with caution and, in most cases, dosages need to be reduced.[13]

Compliance

Compliance and adherence to treatment is crucial, especially as these drugs have a relatively short half-life.[13]

INR

When switching from a VKA to an NOAC, the INR should be allowed to fall to <2.0 before starting the NOAC.[13]

ANSWER 5

Aspirin is often considered in patients who are either not candidates for anticoagulation (eg patients with increased bleeding risk) or are low-risk patients on the basis of a $CHADS_2$/CHA_2DS_2-VASc score. Unfortunately, the evidence for effective stroke prevention with aspirin in AF is weak and should be limited to the few patients who refuse any form of oral anticoagulants.[6]

A meta-analysis[14] confirmed that warfarin, which is considered the standard therapy, is superior to single and combination antiplatelet therapy in the prevention of stroke. Adjusted doses of warfarin and aspirin reduce the risk of stroke by 64% and 22%, respectively.

In the ACTIVE-W trial,[15] warfarin therapy reduced the rate of stroke by 42%, compared with therapy with clopidogrel plus aspirin.

ANSWER 6

Decision-making for prophylaxis of thromboembolism needs to balance the risk of stroke against the risk of major bleeding.

The NOACs offer an alternative to warfarin therapy for selected patients, but, as with all anticoagulants, they can potentially cause serious bleeding. The HAS-BLED score was developed as a practical risk score to estimate the one-year risk for major bleeding in patients with AF.[16]

HAS-BLED scores gives one point each for presence of:

- hypertension (systolic blood pressure >160 mmHg)
- age >65 years
- prior history of stroke or TIA
- prior major bleeding or predisposition to bleeding
- labile INRs (ie unstable/high INRs, time in therapeutic anticoagulation of <60%)
- abnormal liver function – cirrhosis or bilirubin twice upper limit of normal, and aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) three times upper limit of normal

- abnormal renal function – dialysis, transplant, creatinine >200 µmol/L
- alcohol use – more than eight standard drinks per week
- drug use – use of drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) and prednisolone.

A HAS-BLED score of 3 and above means that regular clinical review to monitor bleeding is recommended following the initiation of anticoagulant therapy.

The term 'valvular AF' indicates that AF is related to rheumatic valvular disease (predominantly mitral stenosis) or the presence of prosthetic heart valves. All the major trials involving NOACs excluded patients with valvular AF and generally warfarin is the preferred treatment option in that clinical setting.

ANSWER 7

Procedures that carry a significant risk of bleeding may require temporary cessation of the NOACs or warfarin (Table 3).[17] When the anticoagulants are discontinued in high-risk patients, the interval without anticoagulation should be as short as possible with the risk of thromboembolism balanced against the risk of bleeding. June's skin biopsy carries a very small risk of excess bleeding so she does not need to stop rivaroxaban treatment prior to the biopsy.

Patients on warfarin undergoing procedures with a low risk of bleeding, such as cataract or skin surgery, may continue warfarin with a relatively low target of INR between 1.5 and 1.8. If the risk of bleeding and thromboembolism is high,[17,18] warfarin should be stopped five days before surgery, and bridging therapy with low molecular weight heparin or unfractionated heparin should be considered. If bleeding risk is low but the risk of thromboembolism is high, warfarin may be continued with the INR target between two and three.

ANSWER 8

In contrast to warfarin, patients on NOACs are less likely to require bridging therapy.[19,20] This is because of the relatively short half-life of NOACs, which allows for properly timed, short-term cessation and early re-initiation after surgery. In the case of emergency, surgery should ideally be deferred for 12–24 hours (since the last dose) if possible.[13]

Table 3. Oral anticoagulants and antiplatelet agents[18,21,24]

Drugs	Mechanism of action	Dosage	Stopping medication before surgery
Warfarin	Vitamin K antagonist	Varies across individuals	Withheld for approximately five days
Dabigatran	Direct thrombin inhibitors	• 150 mg twice daily for most patients • 110 mg BD for patients aged >75 years or with ClCr 30–49 ml/min	24 hours: • low bleeding risk and normal renal function 96 hours: • high-bleeding-risk individual and impaired renal function[21]
Rivaroxaban	Factor Xa inhibitor	• 20 mg daily for most patients • 15 mg daily if ClCr 30–49 ml/min • Avoid if ClCr <30 ml/min	24–48 hours[21]
Apixaban	Factor Xa inhibitor	• 5 mg twice daily for most patients • 2.5 mg twice daily for age >80 years, weight <60 kg serum creatinine >133 µmol/L	24–48 hours
Aspirin	Inhibits thromboxane A_2 synthesis by irreversibly acetylating cyclooxygenase-1 in platelets and megakaryocyte	75–325 mg once daily	• Most often can be continued • May need to be stopped 5–7 days before surgery
Clopidogrel	Metabolised in the liver to active compounds that bind covalently to ADP receptors on platelets and reduce platelet activation	75 mg daily	5–7 days prior to surgery
Prasugrel	An ADP receptor antagonist	• 10 mg once daily for adults >60 kg • 5 mg once daily for patients <60 kg	5–7 days prior to surgery
Ticagrelor	Reversible, directly acting inhibitor of the ADP receptor P_2Y_{12}	90 mg twice daily	5–7 days prior to surgery

Some variation exists in the recommended time to cease dabigatran between the European Society of Cardiology guidelines[21] and Queensland Health guidelines.[24] The latter guidelines recommend stopping dabigatran for five days in patients with CrCl of 31–50 mL/min and longer than five days (and not to restart) in patients with CrCl <30 mL/min.

ADP, adenosine diphosphate; CrCl, creatinine clearance

If not, then a multidisciplinary team approach including the surgeon, haematologist and cardiologist should be considered, and the risk of bleeding carefully assessed and discussed with the patient and relatives. These should be assessed on a case-by-case basis.

ANSWER 9

The timing to restart the NOACs after surgery will depend on multiple factors. These include the factors mentioned above, along with the type of surgery and the ability to achieve immediate haemostasis. For procedures with immediate and complete haemostasis, NOACs can be resumed six to eight hours after intervention.[13]

In many surgical interventions, the resumption of anticoagulation within 48–72 hours may carry a significant bleeding risk and is therefore better off deferred. Once NOACs are restarted, maximal anticoagulation will be obtained within two hours.[13]

ANSWER 10

Currently, availability of the antidotes for NOACs is limited in Australia. Certain centres may have access to the drug mainly for clinical trial purposes. NOACs have relatively short half-lives and most of the bleeding complications can be managed by cessation of the drug and general haemostatic measures.[21] Recently, idarucizumab was approved by the US Food and Drug Administration (FDA) and is now licensed for use in the US as a reversal agent for dabigatran.[22] Andexanet Alfa[23] is still awaiting FDA approval for use in reversing the anticoagulant effect of factor X inhibitors.

Idarucizumab and andexanet alfa are expensive and supportive management of bleeding with haemodynamic resuscitation has a major role in the non–life-threatening, non-urgent situations of bleeding. It is likely that in Australia, reversal agents for NOACs will be for management of life-threatening major bleeding and for rapidly reversing the anticoagulant effects of NOACs for emergency surgery or urgent procedures.

CONCLUSION

June responded very well to supportive measures. Rivaroxaban was recommenced prior to discharge from hospital on day five.

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CASE 6

TIM FEELS WORN OUT

Tim, aged 46 years, and his family have been attending your practice for the past six years. He has only been an occasional patient and been in good general health. Today, he presents requesting a 'check-up'. His father has recently been diagnosed with a lymphoma. Tim reports that he feels 'a bit worn out' but does not have any other concerns apart from an old knee injury.

QUESTION 1

What further information should you obtain from Tim? What physical examination would you perform and what investigations would you order?

FURTHER INFORMATION

You update Tim's file and review his past medical and social history. He is an ex-smoker and drinks four beers twice a week. Tim works full time at the local hardware shop.

On examination, you find that Tim is slightly overweight; his body mass index (BMI) is 28 kg/m^2. His blood pressure is 140/86 mmHg, and cardiovascular, respiratory and abdominal examinations are normal. His mood and affect are normal.

You order a fasting full blood evaluation (FBE), urea, electrolytes and creatinine (UEC), liver function tests (LFTs), thyroid stimulating hormone (TSH), blood glucose and lipid levels.

Tim returns the following week for the results. All of the tests are in the normal range except for alanine aminotransferase (ALT) and aspartate aminotransferase (AST), which are elevated (ALT = 68; AST = 44). On further questioning, Tim reports that he had a period of injecting drug use when he was 20–22 years of age, and had a tattoo in Bali in 1998.

QUESTION 2

What additional investigations would you order now?

FURTHER INFORMATION

You order full hepatitis B and C serology (after obtaining informed consent from the patient), iron studies and ultrasonography of the upper abdomen.

The abdominal ultrasound shows mild fatty liver. Hepatitis B surface antigen (HBsAg) is negative, but hepatitis B core antibody (anti-HBc) and hepatitis B surface antibody (anti-HBs) are positive, indicating past infection and clearance of hepatitis B. Hepatitis C virus (HCV) antibody is positive with a positive HCV ribonucleic acid (RNA), indicating chronic hepatitis C infection.

QUESTION 3

Tim returns for his results. What are you going to tell him?

FURTHER INFORMATION

Tim is upset about the diagnosis but relieved when you advise him that hepatitis C is very rarely transmitted sexually.[1]

You discuss the availability of new 'direct acting antivirals' (DAAs), which were listed on the Pharmaceuticals Benefits Scheme (PBS) in March 2016.

QUESTION 4

What further investigations will you perform for Tim?

FURTHER INFORMATION

You refer Tim for a FibroScan at the local liver outreach clinic, a service provided by the local health district. At the same time you request a blood test for hepatitis C genotype and hepatitis C quantitative RNA. The results come back showing that Tim has genotype 1a with a viral load of 9,300,000. The FibroScan report gives a 'liver stiffness' reading of 7.8 kPa, which is consistent with early fibrosis.

Tim returns for his results. He is very keen to have treatment for hepatitis C with the new medications available on the PBS. Tim asks how he can access the new treatment.

QUESTION 5

How would you respond to Tim's query about access to new treatments?

FURTHER INFORMATION

You recently attended an HCV update and feel confident to prescribe treatment for Tim. Checking the consensus guidelines for hepatitis C,[2] you advise Tim that he has a better than 90% chance of clearing HCV if he has a 12-week course of treatment. You provide him with treatment information and schedule a long appointment.

QUESTION 6

What are the steps that you need to follow in order to treat Tim with the new DAAs?

FURTHER INFORMATION

Tim returns to your office for his appointment. He qualifies for treatment under the PBS. You call the Authority Prescription Application Service and obtain an authority prescription for sofosbuvir 400 mg daily + ledipasvir 90 mg daily co-formulated as a single pill (Harvoni) to be taken once daily for 12 weeks. Tim understands the importance of good adherence to the regimen and agrees to contact you if he experiences significant side effects.

QUESTION 7

What follow-up does Tim need?

CASE 6 ANSWERS

ANSWER 1

It is important to explore Tim's concerns and reasons for today's consultation. It seems that his concern about his father's illness has prompted his visit. He also reports being 'a bit worn out', so it would be useful to explore this further. This consultation also provides a good

opportunity to discuss Tim's general health and lifestyle issues, and to review appropriate health screening as per The Royal Australian College of General Practitioners' (RACGP's) recommendations.[3]

It is important to take a thorough history and perform a physical examination prior to ordering investigations. NPS MedicineWise has produced flowcharts for the assessment of a patient presenting with fatigue, which suggests investigations should be clearly based on thorough history and examination.[4]

ANSWER 2

Tim's results are consistent with hepatitis (liver inflammation). Additional investigations should be carried out to confirm/exclude possible causes of Tim's test results:

- viral hepatitis – Hepatitis B and C – confirm with serology
  - HBsAg
  - anti-HBc
  - anti-HBs
  - HCV antibody
- non-alcoholic fatty liver disease – suggested by a history of obesity and changes on ultrasound
- alcoholic liver disease – associated with alcohol use
- drug-induced hepatitis – check use of current medication, including over-the-counter medications, herbal medicines and supplements. Reactions can be predictable (such as paracetamol overdosing) or idiosyncratic[2]
- hereditary conditions – haemochromatosis – check iron studies
- autoimmune hepatitis – uncommon (testing is complex, so it is important to discuss this with your laboratory or specialist).

ANSWER 3

You should advise Tim that he has chronic hepatitis C infection, probably acquired during his period of injecting drug use (less likely from the tattoo in Bali). You discuss his concerns about infectivity (low), natural history and treatment.[1] It is very important to review his emotional state and mood following this potentially very distressing diagnosis. You offer him a follow-up long appointment to further discuss treatment options. You also refer him to the Hepatitis Australia website (refer to 'Resources for patients'). ASHM has useful information about how to inform patients of a positive HCV diagnosis.[5,6]

Notably, of the estimated 185,740 people thought to be living with chronic hepatitis C infection in Australia, 75% have been diagnosed.[7]

ANSWER 4

You should order a hepatitis C genotype and viral load (HCV quantitative RNA). Most patients in Australia are genotypes 1 (50–55%), 3 (35–40%) and 2 (5–10%), which can be treated with interferon-free regimens on the PBS.[8] Genotypes 4–6 are uncommon, but currently require the use of interferon-containing regimens.[2] Patients with genotype 4–6 should therefore be referred to specialist care.

All patients should be investigated by a non-invasive measure of liver fibrosis, including liver elastography (eg FibroScan) or by serum biomarker (eg APRI score, FIB-4 HepaScore). Some patients will have had a liver biopsy performed previously, but this is rarely performed now unless there is diagnostic uncertainty.

Figure 1. Portable FibroScan machine

Increasingly, liver fibrosis is measured using FibroScan (Figure 1), which is a non-invasive test of liver fibrosis. This investigation can be performed in most liver clinics around Australia. It is likely to become more available in 2016 with an anticipated listing on the Medicare Benefits Schedule (MBS).

Estimates of the distribution of liver disease suggest that only about 7% of patients have cirrhosis (F4), which always requires specialist review, 13% have advanced fibrosis (F3), while the remaining 70% have earlier stage disease (F0–2).[8]

All patients with cirrhosis need specialist referral. They will need additional investigations and regular screening for complications such as hepatocellular carcinoma (HCC). Patients with cirrhosis will often need longer and sometimes more complex therapy. Documentation of the presence or absence of cirrhosis is required in determining PBS eligibility.[2]

Risk factors for the development of cirrhosis include length of infection, male sex and the presence of comorbidities such as alcohol abuse, viral co-infection (hepatitis B virus [HBV], and human immunodeficiency virus [HIV]). Signs and symptoms of cirrhosis include a stiff liver edge, spider naevi, ascites, oedema and jaundice. Common investigations suggesting cirrhosis include a low albumin and/or a low platelet count.[1] It is important to note that a normal ALT and AST does not exclude cirrhosis.

ANSWER 5

The PBS listing allows the new hepatitis C medicines to be prescribed by gastroenterologists, hepatologists or infectious diseases (ID) physicians who are experienced in the treatment of chronic HCV infection, as well as by general practitioners (GPs) in consultation with

one of these specialists. Consultation can be by phone, fax, or email. Ideally, the GP will have some experience and training in order to prescribe. Training is available online through the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM) that runs regular prescriber updates. A proforma that GPs can use to send their treatment plan for specialist review is available on the ASHM website (refer to 'Resources for doctors').

Patients with earlier disease can generally be treated with 12 weeks of combination DAA therapy with a high likelihood of cure.[2] Patients with comorbidities such as renal disease or co-infections (HBV, HIV) should be referred for specialist review. Note that patients should avoid pregnancy and breastfeeding during DAA treatment.

Existing medication should be checked for drug–drug interactions using online tools such as that provided by the University of Liverpool drug interaction website (refer to 'Resources for doctors').

DAA selection and dosage may need to be modified, or current medication reviewed prior to treatment.

ANSWER 6

As Tim has earlier stage fibrosis, normal renal function, no drug–drug interactions and has genotype 1a, you have enough information to safely prescribe for him (using Table 1 as a reference). You forward the clinical information to the local liver clinic and the specialist fives his approval to commence treatment.

At this stage you are ready to complete a PBS authority prescription. Table 2 lists the PBS medications currently available. Note that additional medication will be available in the future, so you should consult with the latest guidelines regarding recommended treatments.[2]

Table 1. Summary of the steps in prescribing DAAs in a GP setting[9]

	GP	Specialist review if …
Step 1	Confirm chronic HCV infection	
Step 2	Check HCV genotype and viral load	Genotype 4,5,6
Step 3	Could they have cirrhosis?	Cirrhosis
Step 4	Detect other causes of liver disease	HIV, HBV
Step 5	Detect other major co-morbidities	Renal impairment
Step 6	Review previous HCV treatment	Treatment failure of DAAs
Step 7	Review drug interactions	Complex interactions
Step 8	Consult with specialist	
Step 9	Treat	Major adverse events
Step 10	Monitor and follow up	Treatment failure of DAAs

Table 2. PBS medications for chronic hepatitis C infection for patients without cirrhosis or previous treatment failure[2]

Genotype	Treatment for 12 weeks (all oral treatment)	Notes
1	Sofosbuvir 400 mg daily + ledipasvir 90 mg daily (*Harvoni*) or Sofosbuvir (*Sovaldi*) 400 mg daily + daclatasvir (*Daklinza*) 60 mg daily	1 pill daily 2 pills daily
2	Sofosbuvir (*Sovaldi*) 400 mg daily + ribavirin (*Ibavyn*) 1000/1200 mg daily (weight-based)	1 sofosbuvir daily and ribavirin twice a day
3	Sofosbuvir (*Sovaldi*) 400 mg daily + daclatasvir (*Daklinza*) 60 mg daily	2 pills daily

If the patient is using ribavirin (genotype 2), they will require additional tests such as an electrocardiogram (ECG) to exclude ischaemic heart disease, as they may develop anaemia.[2] Ribavirin is also a teratogen, so the patient will need to use two forms of contraception.

ANSWER 7

Patients do not require intensive monitoring during treatment unless they have significant comorbidities or other difficulties that may affect adherence. It is probably reasonable to schedule four-weekly appointments with an FBE and LFTs for the first few weeks.[2] At these visits you are checking for side effects, compliance and possible drug–drug interactions if the patient is taking any prescribed, recreational or over-the-counter medications. Patients taking ribavirin need more regular monitoring depending on their level of anaemia.[2]

The aim of treatment is virological cure. This is sustained virological response (SVR 12), defined as undetectable plasma HCV RNA at least 12 weeks after treatment has ceased. Unlike interferon-based treatment, regular monitoring of HCV RNA during treatment is not generally needed unless you have concerns about compliance.[2]

Common side effects of treatment with DAAs include headache, fatigue and nausea; however, few patients have to cease treatment because of side effects. Therapy with ribavirin has more side effects including anaemia, rash, cough, shortness of breath, insomnia and anxiety.

Patients need referral if DAA therapy fails, or if they have ongoing signs of liver disease or persistently abnormal LFTs after treatment.

CONCLUSION

You schedule a review at one month with an FBE and LFTs. At that visit Tim is feeling well. You reinforce the importance of good compliance with the regimen. He sees you monthly through the treatment. Three months after completing treatment his final HCV qualitative RNA test is negative, indicating cure. Unless Tim has any future exposures to HCV or ongoing signs of liver disease, he does not need any further testing.

RESOURCES FOR PATIENTS

- Hepatitis Australia, www.hepatitisaustralia.com

RESOURCES FOR DOCTORS

- Australian Society for HIV, Viral Hepatitis and Sexual Health Medicine (AHSM) has various resources for general practitioners including 'Remote consultation request for initiation of hepatitis C treatment template', www.ashm.org
- Decision-making in hepatitis C, www.ashm.org.au/resources/Pages/1976963398.aspx
- University of Liverpool drug interaction tool, www.hep-druginteractions.org

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ACTIVITY ID: 41339

BLOOD DISORDERS

This unit of *check* is approved for six Category 2 points in the RACGP QI&CPD program. The expected time to complete this activity is three hours and consists of:

- reading and completing the questions for each case study
  - you can do this on hard copy or by logging on to the *gplearning* website, http://gplearning.racgp.org.au
- answering the following multiple choice questions (MCQs) by logging on to the *gplearning* website, http://gplearning.racgp.org.au
  - you must score ≥80% before you can mark the activity as 'Complete'
- completing the online evaluation form.

You can only qualify for QI&CPD points by completing the MCQs online; we cannot process hard copy answers.

If you have any technical issues accessing this activity online, please contact the *gplearning* helpdesk on 1800 284 789.

If you are not an RACGP member and would like to access the *check* program, please contact the *gplearning* helpdesk on 1800 284 789 to purchase access to the program.

CASE 1 – LEROY

Leroy, 68 years of age, has a history of hypertension, diabetes mellitus and Graves' disease. He has been able to manage his diabetes through lifestyle changes, adhering to regular exercise and a healthy diet. Leroy does not smoke and has one or two glasses of wine at the weekends. He is on carbimazole for his Graves' disease and perindopril for his hypertension. Leroy attends today because he has been experiencing fatigue, weakness and dyspnoea. On examination, you find that Leroy has an irregular pulse, so you order an electrocardiogram (ECG), which shows that he has atrial fibrillation. He has no signs of decompensated heart failure. As part of your follow-up, you assess Leroy's risk of thromboembolism by calculating his CHA_2DS_2-VASc score.

QUESTION 1

From the information in Leroy's history, his CHA_2DS_2-VASc score is:

A. 1

B. 2

C. 3

D. 4

QUESTION 2

Given Leroy's CHA_2DS_2-VASc score, which of the following statements is correct?

A. Anticoagulant treatment may have a net clinical benefit for Leroy.

B. Leroy's CHA_2DS_2-VASc score indicates that he is at a low risk of stroke.

C. Leroy's CHA_2DS_2-VASc score indicates that he is at a moderate risk of stroke.

D. Anticoagulant therapy is not indicated in Leroy's case.

QUESTION 3

Factor(s) included in the assessment of Leroy's bleeding risk is/are:

A. his age and history of hypertension

B. his history of diabetes

C. his history of Graves' disease

D. All of the above

QUESTION 4

When considering anticoagulant options for Leroy, which of the following statements is true?

A. The new oral anticoagulants (NOACs) have been associated with a greater risk of major bleeding, compared with warfarin.

B. The risk of adverse drug interactions is similar for NOACs and warfarin.

C. An antibody fragment that can reverse the effects of rivaroxaban is now available for use in Australia.

D. Most of the NOACs would be contraindicated if Leroy had an eGFR of <30 mL/min.

FURTHER INFORMATION

Leroy has been a keen jogger for many years but in the past six months he has been having joint problems. He has been advised that might need knee replacement surgery.

QUESTION 5

Essential blood tests that should be performed initially to identify factors that will influence patient blood management include:

A. liver function tests (LFTs)

B. iron studies

C. vitamin B12 levels

D. folate levels.

FURTHER INFORMATION

Leroy has blood tests to assess his iron stores and risk of anaemia.

QUESTION 6

According to current guidelines, which of the following haemoglobin levels (g/L) and serum ferritin levels (µg/L) are most consistent with iron deficiency anaemia?

A. 126 and 34

B. 131 and 25

C. 128 and 14

D. 133 and 37

FURTHER INFORMATION

Leroy's blood test results show that his haemoglobin level is normal (155 g/L), but his serum ferritin is markedly elevated at 800 µg/L. Further testing rules out viral hepatitis, but confirms the presence of a C282Y homozygous mutation, suggesting *HFE*-related hereditary haemochromatosis (HH).

QUESTION 7

Given these findings, what is the recommended schedule for venesection and review?

A. Weekly, review at 10 weeks

B. Four weekly, review at six months

C. Six weekly, review at six months

D. Three monthly, review at six months

CASE 2 – TRIS

Tris, 35 years of age, presents with ongoing symptoms of lethargy, muscle and joint pain, and upper abdominal discomfort. You take a thorough history, which reveals that Tris experimented briefly with intravenous drug use when he was younger. Physical examination is normal. Subsequent pathology tests show that Tris has hepatitis C, genotype 3.

QUESTION 8

According to the Pharmaceutical Benefits Scheme (PBS), the recommended treatment for Tris is:

A. Sofosbuvir 400 mg daily + ledipasvir 90 mg, 1 pill daily for 12 weeks

B. Sofosbuvir 400 mg daily + ledipasvir 60 mg, 2 pills daily for 12 weeks

C. Sofosbuvir 400 mg daily + ribavirin 1000/1200 mg daily (weight-based), 1 sofosbuvir daily and ribavirin twice daily for 12 weeks

D. Sofosbuvir 400 mg daily + daclatasvir 60 mg daily, 2 pills daily for 12 weeks

QUESTION 9

The aim of treatment is virological cure. This is defined as undetectable hepatitis C virus ribonucleic acid (RNA) at least:

A. 10 weeks after cessation of treatment

B. 12 weeks after cessation of treatment

C. 14 weeks after cessation of treatment

D. 20 weeks after cessation of treatment

CASE 3 – CARLA

Carla, 30 years of age, comes to see you because a former partner contacted her last night to tell her that he had been diagnosed with chronic hepatitis B. Carla, distressed and barely able to speak through her tears, asks if she can be tested for hepatitis B. The results show:

- Hepatitis B surface antigen (HBsAg): Positive
- Hepatitis B surface antibody (anti-HBs): Negative
- Hepatitis B core antibody (anti-HBc): Positive

Further testing shows:

- Hepatitis B DNA (viral load): 25,000 IU/mL
- Hepatitis B e-antigen (HBeAg): Positive
- Hepatitis B e-antibody (anti-HBe): Negative
- Liver function tests: Normal

QUESTION 10

How should Carla be managed?

A. Carla should be commenced on antiviral treatment.

B. Carla should be referred to a specialist for further assessment and consideration of antiviral treatment.

C. Carla does not need antiviral treatment but should be monitored every three months.

D. Carla does not need antiviral treatment but should be monitored every six to 12 months.

check

Independent learning program for GPs