check

Independent learning program for GPs

Unit 502 January – February 2014

Dermatology

RACGP

www.racgp.org.au/check

Subscriptions

For subscriptions and enquiries please call 1800 331 626 or email check@racgp.org.au

Published by

The Royal Australian College of General Practitioners
100 Wellington Parade
East Melbourne, Victoria 3002, Australia
Telephone 03 8699 0414
Facsimile 03 8699 0400
www.racgp.org.au

ABN 34 000 223 807
ISSN 0812-9630

check

Independent learning program for GPs

Dermatology

Unit 502 January – February 2014

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

Skin is the largest organ in the body and it is frequently damaged. It has been reported that there are more than 3000 skin diseases.[1] A study estimating the global burden of disease attributable to skin disease across 187 countries, from 1990 to 2010, reported that fungal skin diseases, other skin and subcutaneous diseases and acne were amongst the top 10 most prevalent conditions worldwide in 2010.[2] Eight skin conditions fell into the top 50 most prevalent diseases globally and skin conditions were the fourth leading cause of non-fatal disease burden in all countries independently of socioeconomic status.[2]

Skin diseases may carry significant mortality and morbidity. When considering the burden of skin disease it is important to also consider the psychological, social and financial consequences of skin disease. For example, Australia has the highest incidence of skin cancer in the world[3] and in 2009, melanoma of the skin was the fourth most commonly diagnosed cancer in Australia after prostate, bowel and breast cancer.[4] Other chronic conditions, such as eczema and psoriasis, are associated with various morbidities affecting health status and quality of life.

Common skin conditions include rashes and rosacea, warts, moles, skin tags, acne, psoriasis eczema, skin cancers and age spots. Clinicians also have to deal with common hair problems (e.g. baldness, scalp psoriasis) and nail problems (e.g. ingrown finger or toenails, and fungal and bacterial infections).

This unit of check will consider a range of common dermatology presentations to general practice and consider new management options where relevant.

LEARNING OUTCOMES

At the completion of this unit, participants will be able to:

- outline appropriate examinations and investigations, including differential diagnosis, for a person presenting with a melanoma-like skin lesion
- predict possible complications that may arise with eczema and how these could be managed
- explain why psoriasis is more than just a skin problem
- describe management options for the treatment of fungal nail infections
- list currently available treatment approaches and potential success rates for management of warts.

AUTHORS

Dr Ian Wardale-Greenwood MBBS, FRACS, Master of Medicine in the field of skin cancer, has been a general practitioner for the last 40 years with experience in skin cancer surgery during this time. He is currently a practitioner in skin cancer management.

Dr Philip Clarke BMedSc, MBBS, FRACGP, DFM, DDSc, FAAD is a senior clinical lecturer at the University of Tasmania. He conducts dermatology research in Launceston and runs the wound clinic at the Launceston General Hospital. Since 2001 he has also had a specialist dermatology practice in Launceston.

Dr Carolyn Royse MMBS, FRACGP has been in general practice for the more than 18 years and currently practices at the Nillumbik Medical Centre in Eltham, Victoria. She has a particular interest in cosmetic procedures including botox, juvederm, laser procedures for skin conditions and in medical education. Carolyn is a clinical lecturer at the University of Melbourne, Department of Medicine.

PEER REVIEWERS

Dr Catherine Reid FRACP FACD is a consultant dermatologist and formerly Head of Dermatology, Royal Adelaide Hospital, South Australia. She is on the Therapeutic Guidelines expert groups for Dermatology and Antibiotics and was Honorary Secretary of the Australasian College of Dermatologists.

Dr Miranda Sandars MBBS, DRANZCOG, FRACGP has worked full time as a general practitioner since 1999. She works at in the inner Melbourne suburb of North Carlton, enjoying a rich mix of clinical problems and presentations, as well as undertaking minor procedures, shared maternity care and regular aged care facility and home visits. Miranda enjoys the variety and challenges of providing best possible medical care for patients and families of all ages, with any acute or chronic, straightforward or complex conditions. In addition to clinical practice, she has worked on expert writing groups for titles in the Therapeutic Guidelines series and on some educational and advisory boards, contributing her GP perspective.

REFERENCES

1. Bickers DR, Lim HW, Margolis D et al. The burden of diseases: 2004: a joint project of the American Academy of dermatology Association and the society for the Investigative dermatology. J Am Acad Dermatol. 2006;55:490–500.
2. Hay RJ, Johns NE, Williams HC et al. The global burden of skin disease in 2010: An analysis of the prevalence ad impact of skin conditions. J Invest Dermatol. doi:10.1038/jid.2013.446 (epub ahead of print).
3. Australian Institute of Health and Welfare and Australasian Association of Cancer Registries 2004. Cancer in Australia 2001. AIHW cat. no. CAN 23. Canberra, AIHW.
4. Australian Institute of Health and Welfare & Australasian Association of Cancer Registries 2012. Cancer in Australia: an overview, 2012. Cancer series no. 74. Cat. no. CAN 70. Canberra, AIHW.

GUIDE TO ABBREVIATIONS AND ACRONYMS IN THIS UNIT OF *CHECK*

ABCDE	Assymetry, Border irregularity, variable Colour, Diameter greater than 6 mm and Evolving	CLND	complete lymph node dissection	3R	Red, raised lesion, with Recent change
AHM	amelanotic/hypomelanotic melanoma	EFG	Elevated, Firm on palpation, and Growing	SLNB	sentinel lymph node biopsy
BSL	blood sugar levels	FBC	full blood count	TGA	Therapeutic Goods Administration
C&E	creatinine and electrolytes	HPV	human papillomavirus		
		LFT	liver function tests		

CASE 1

DAVID, MARY, DON AND PATRICK'S SKIN LESION PRESENTATIONS

You work in two busy practices in the northern suburbs of a major metropolitan area and several interesting skin cases have presented recently, including:

1. David, aged 38 years, presented for a routine skin examination and mentioned his concern about a small, recent onset, inflamed papule on the distal right forearm. The lesion measured 3 x 2 mm and dermoscopy showed no reticular network but some atypical vessels were present.
2. Mary, aged 59 years, presented with a 5-mm diameter red nodule situated in an old melanoma scar on the right side of her neck. The melanoma had been excised 11 years ago and had a Breslow thickness of 0.64 mm. She also had a thin melanoma excised from her right thigh 27 years ago. The area in the neck scar had been itchy over the last 4 months and had changed significantly over a period of a few weeks, rapidly developing into the nodule. Dermoscopy showed a pale pink area in the centre of the lesion together with regular, well-focused, circumferential hairpin vessels. No peripheral network remnants were evident.
3. Don, aged 82 years, had just returned from a holiday in China where he had done a lot of walking. He had been wearing a new pair of shoes and presented with an ulcerated region over a prominent hallux valgus on his right foot. The ulcer was treated and healed slowly over a 2-month period; however, it then reappeared and was thought to be due to his shoe rubbing on the area.
4. Patrick, aged 54 years, presented because his wife had incidentally noticed a small swelling lying deep to a small, pale, innocent-looking mole on his left deltoid region. Dermoscopy revealed a featureless naevus with a small area of negative network. A small, indurated, localised area was palpable, lying directly below the naevus, presumably within the dermis.

QUESTION 1

What are the likely differential and provisional diagnoses for the individual cases?

QUESTION 2

What is the place of dermoscopy in the diagnosis of amelanotic or hypopigmented lesions?

QUESTION 3

How would you establish a definitive diagnosis?

QUESTION 4

What are these lesions?

QUESTION 5

How would you manage these lesions?

QUESTION 6

What are the red flags to watch out for with AHM?

CASE 1 ANSWERS

ANSWER 1

To assist with making differential and provisional diagnoses, a medical history should be taken. The history should include specific risk factors, previous episodes of skin cancer and melanoma, the degree of sun exposure (particularly during childhood and early adulthood), previous episodes of sunburn (including peeling), family history, a general medical summary, medications and allergies.

If on a comprehensive skin examination from head to toe, any suspicious lesion is detected, it is very important to determine whether it is of recent onset or longstanding, and whether it has undergone any recent change. The size, shape, colour and texture of the lesion should be noted, together with the site and dermoscopic features. Only biopsy or excision will provide a histological and definitive diagnosis. If the lesion is clinically suspicious, even without dermoscopic assessment, a biopsy should be done or the patient referred to a specialist.

Patients frequently present complaining of a new or recent onset skin lesion or of a change in an existing lesion. Any patient concern should immediately arouse suspicion. Change is a prominent feature of all skin malignancies, including melanoma, and it includes changes in size, shape, colour and surface, the onset of bleeding, itching, inflammation or soreness, as well as the development of crusted or scar-like features.

Differential and provisional diagnoses for the individual cases include:

1. **David's red to pink macule or papule:** solar keratosis, dermal naevus, hypopigmented common naevus, and amelanotic/hypomelanotic melanoma (AHM).
2. **Mary's reddish firm nodule:** haemangioma (Campbell de Morgan spot), intraepidermal carcinoma, squamous cell carcinoma, keratoacanthoma, basal cell carcinoma, Merkel cell carcinoma, classical Spitz naevus, pyogenic granuloma, dermal melanoma metastases and AHM.
3. **Don's ulcerating non-healing lesion:** venous or arterial ulcer, diabetic ulcer, granulating traumatic ulcer, ulcerating squamous cell or basal cell carcinoma and AHM.
4. **Patrick's localised dermal induration:** dermatofibroma, neurofibroma, sclerosing basal cell carcinoma, hypertrophic scar and desmoplastic melanoma.

All the above skin lesions are either non-pigmented or hypopigmented.

Other presentations within this group of lesions include:

1. erythematous patch or plaque: eczema, psoriasis, common wart, irritated seborrhoeic keratosis, superficial basal cell carcinoma and AHM
2. nail lesions: ingrowing toenail not responding to treatment, any nail-deforming lesion including onychomycosis, and ulcerating nailbed lesions including squamous cell carcinoma and AHM
3. the pink or red **non-pigmented 'ugly duckling'** lesion, which is a lesion that is different from and stands out from the other naevi in the region.

AHM has to be considered in the differential diagnoses in each of the above presentations. AHM is difficult to diagnose as it can mimic so many different benign and malignant lesions, and the face and the foot are notorious regions for misdiagnoses.[1]

ANSWER 2

The use of dermoscopy (epiluminescent microscopy of the skin) by trained individuals has been shown to significantly increase the diagnostic accuracy for melanoma when compared with the naked eye examination.[2] However, its main use is for assessing pigmented lesions and its accuracy is significantly reduced with amelanotic or hypopigmented lesions.[3] Dermoscopy is not widely used in general practice, and medical history and skin examination are the key aspects of the clinical assessment. If a clinically suspicious lesion is detected a biopsy should be done or the patient referred to a specialist.

In the amelanotic and hypopigmented group of lesions very little or no pigmentation or reticular network is present.

Additionally:

- The ABCDE (Asymmetry, Border irregularity, variable Colour, Diameter greater than 6 mm and Evolving) criteria together with other algorithms or dermoscopic features routinely used for melanocytic lesions are rarely positive, and often they can fail to detect nodular melanoma.[4]
- The EFG (Elevated, Firm on palpation, and Growing continuously over the last month) rule was developed specifically for nodular lesions, and it covers their most relevant clinical features.[5]
- The 3R (Red, Raised lesion with Recent change) criteria have also been developed for nodular amelanotic lesions. However, we do not yet know if the use of the EFG and 3R diagnostic aids are helping to detect nodular melanoma at an earlier stage of development.[6]
- The Chaos and Clues algorithm[7] has been developed mainly for pigmented skin lesions but it also addresses the amelanotic or hypopigmented lesions with the 'Clue present' features of white lines, eccentric white or pink structureless areas and polymorphous vessels, and the 'Clue not present' feature of changing lesions in adults.

For truly amelanotic melanoma where there are no pigmented structures, diagnosis depends critically on vascular patterns, which are visible only with dermoscopy.[1] Vascular structures may not be diagnostic of AHM, but they can indicate a high degree of suspicion, and 11% of AHM have been reported as having no visible vessels.[3]

We should note that the ultimate aim of dermoscopy is not to diagnose melanoma, but to determine the need for a biopsy.[8]

ANSWER 3

Excision biopsy of any suspicious amelanotic or hypopigmented lesion should be performed, as it is the only way that a definitive diagnosis can be made. Complete removal of the lesion should be carried out with a 2 mm margin.[9] If it is impractical to excise the

whole lesion, as in Don's case, then a partial biopsy (punch, incision or shave) from the most suspicious area of the lesion would be appropriate.[10] A higher percentage of shave biopsies tend to be performed for red amelanotic melanomas, leading to a significant proportion of positive deep margins and incomplete staging on histological examination.[11]

If the biopsy is positive for melanoma, the results should be delivered to the patient face-to-face in an empathetic manner. Plenty of time should be allocated for this, and a general treatment plan should be provided. Good communication with the patient and their immediate family is essential.

The biopsy results in each of these cases confirmed the presence of AHM:

1. **David:** a Clark level 4, spitzoid melanoma, with a Breslow thickness of 1.05 mm and a single dermal mitotic figure.
2. **Mary:** a Clark level 4, superficial spreading melanoma, with a Breslow thickness of 2.5 mm and a high mitotic rate of 17/mm^2.
3. **Don:** a Clark level 4, acral malignant melanoma with ulceration and no report as to mitotic rate.
4. **Patrick:** a Clark level 4, desmoplastic melanoma with a Breslow thickness of 3.1 mm and a mitotic rate of 1/mm^2.

ANSWER 4

David, Mary, Don and Patrick's lesions are AHM, which constitutes 2–8% of all melanomas.

The great majority of AHM are clinically amelanotic but on dermoscopic examination may have some subtle peripheral pigmentation. These latter lesions, therefore, are classified as hypomelanotic melanoma. Truly amelanotic melanomas are quite rare, constituting less than 2% of all melanomas.[12]

It has been proposed that nodular melanomas, including nodular AHM, may originate from dermal stem cells, thereby displaying a vertical growth phase from the outset.[13] They demonstrate a more rapid rate of growth,[14] have a more biologically aggressive behaviour,[15] an increased number of mitoses[16] and a propensity to metastasise early, emphasising the importance of early recognition and excision.[17]

AHM are great mimickers, which represents an important diagnostic challenge for clinicians,[18] and when the Breslow thickness is taken into account, they are comparable in lethality to classically pigmented melanomas.[10] Note that all of the above cases were Clark level 4 lesions that had invaded down to the reticular dermis; hence their chance of producing metastases was quite high.

ANSWER 5

After the biopsy results are obtained these cases should be referred to a specialist unit for wider excision and, if appropriate, for consideration of a sentinel lymph node biopsy (SLNB) for prognosis and staging. The Australian and New Zealand guidelines[9] for the management of melanoma recommend that SLNB should be discussed with patients who have melanomas of 1 mm in thickness. It is most important to inform the patient that SLNB will not improve their overall chances of survival, but a positive SLNB followed by early complete lymph node dissection (CLND) can provide a better 5-year survival rate of 72.3%, versus 52.4% when CLND is performed after the regional lymph nodes have become clinically apparent.[10] SLNB and lymphatic mapping should be done before wide excision.[9]

Long-term management initially involves 3-monthly follow-up examinations, with the GP visit alternating with the specialist unit. The clinician should examine the melanoma scar, the intransit region to the draining nodes, the regional and other lymph nodes, and the liver and spleen. In a meta-analysis,[19] ultrasound examination of lymph nodes was consistently more accurate than palpation for the detection of lymph node metastases, and in many instances the patient will present after they have discovered a new regional lymph node swelling.

It is most important to manage the patient in an appropriate fashion. They are frequently very anxious and have many spontaneous and internet-derived questions to be answered, which is difficult in a busy specialist unit. The GP can be the main point of contact and support and should provide adequate time to answer any questions in a sincere and empathetic manner.

The public is becoming much more aware of the red flags for unusual skin lesions (e.g. pigmented naevi) but the public and many GPs are generally unfamiliar with the multiple presentations of the AHM subtype of melanoma, so public education programs and continuing medical education programs for GPs should be encouraged.

Patient education in frequent skin self-examinations and the use of self-photography in high-risk groups is critical, as nodular melanomas may arise and grow rapidly between routine physician screenings.[20]

Prompt presentation should also be encouraged and, if patients are being referred to a specialist centre, the GP should make sure that they have urgent access and treatment.

ANSWER 6

In general, AHM presentations can be very variable and subtle, and any patient concern about a particular lesion, a history of any new lesion, of a changing lesion, or of itchiness, bleeding, inflammation or soreness, should raise a red flag and be considered to be very relevant.

Additional considerations are described below.

- Be aware that recent onset, small, subtle, erythematous macule, papule or plaque can frequently have surface scale and resemble eczema or other benign amelanotic or hypomelanotic lesions. Have a low threshold for biopsy.
- With any firm, recent onset, red nodule, one must suspect a malignant lesion and urgent biopsy is required. It could be an AHM or a Merkel cell carcinoma, as well as one of the other skin malignancies. Be aware that an early AHM can masquerade as a haemangioma (Campbell de Morgan spot) or as a pyogenic granuloma.
- For all non-healing ulcers, biopsy early, not late.
- Any recent onset dermal lump or localised induration should be biopsied.

- Any of the non-pigmented dermoscopic features should be noted, including a pink or red background, polymorphous vessels and white lines.
- For any destructive or deforming nail lesion that persists despite treatment, consider biopsy early.
- Look for any traces of pigment or other signs of melanoma before any destructive therapy, such as cryotherapy or laser treatment, and if any doubt exists send tissue for histology. This applies particularly to acral or plantar warts and to any lesion where AHM cannot be ruled out with certainty.[21]
- Do not forget the pink or red non-pigmented 'ugly duckling' lesion.

CONCLUSION

It is important to appreciate that the history of any new or rapidly changing lesion, along with a very high degree of suspicion, is extremely important for the 'very early diagnosis' of this very dangerous lesion (i.e. AHM). It can present in many different ways, mimicking many other conditions. When used by trained individuals, dermoscopy can be important in the assessment of suspicious amelanotic or hypopigmented lesions, and the EFG, the 3R and the Chaos and Clues algorithms address the various diagnostic features. It is most important that clinicians be vigilant when examining amelanotic or hypomelanotic lesions and that they have a very low threshold for performing full-thickness biopsies – no one has yet died from a biopsy, but many have died from a late diagnosis of AHM.

It is strongly recommended that GPs consider dermoscopic training; some excellent courses are available.

REFERENCES

1. Stoecker WV, Stoltz W. Dermoscopy and the diagnostic challenge of amelanotic and hypomelanotic melanoma. Arch Dermatol 2008;144:1207–10.
2. Vestergaard ME, Macaskill P, Holt PE, Menzies SW. Dermoscopy compared with naked eye examination for the diagnosis of primary melanoma: a meta-analysis of studies performed in a clinical setting. Br J Dermatol 2008;159:669–76.
3. Menzies SW, Kreusch J, Byth K et al. Dermoscopic Evaluation of Amelanotic and Hypomelanotic Melanoma. Arch Dermatol 2008;144:1120–27.
4. Kelly JW, Chamberlain AJ, Staples MP, McAvoy B. Nodular melanoma: no longer as simple as ABC. Aust Fam Physician 2003;32:706–09.
5. Kelly JW. Nodular melanoma: how current approaches to early detection are failing. J Drugs Dermatol 2005;4:790–93.
6. Shaikh WR, Ziong M, Weinstock MA. The contribution of nodular subtype to melanoma mortality in the United States, 1978 to 2007. Arch Dermatol 2012;148:30–36.
7. Rosendahl C, Cameron A, McColl I, Wilkinson D. Dermatoscopy in routine practice – chaos and clues. Aust Fam Physician 2012; 41:482–87.
8. Bystryn JC. Epiluminescence microscopy: a reevaluation of its purpose. Arch Dermatol 2001;137: 377–78.
9. NHMRC. Clinical practice guidelines for the management of melanoma in Australia and New Zealand, 2008. Available at www.nhmrc.gov.au/_files_nhmrc/publications/attachments/cp111.pdf [Accessed 9 January 2014].
10. Thompson JF, Scolyer RA, Kefford RF. Melanoma – a management guide for GPs. Aust Fam Physician 2012;41:470–73.
11. McClain SE, Mayo KB, Shada AL, Smolkin ME, Patterson JW, Slingluff CL, Jr. Amelanotic melanomas presenting as red skin lesions: a diagnostic challenge with potentially lethal consequences. Int J Derm 2012;51:420–26.
12. Giuliano AE, Cochran A, Morton D. Melanoma from unknown primary site and amelanotic melanoma. Semin Oncol 1982;9:442–47.
13. Zalaudek I, Marghoob AA, Scope A et al. The three roots of melanoma. Arch Dermatol 2008;144: 1375–79.
14. Liu W, Dowling JP, Murray WK, et al. Rate of growth in melanomas: characteristics and associations of rapidly growing melanomas. Arch Dermatol 2006;142:1551–58.
15. Richard MA, Grobb JJ, Avril MF et al. Melanoma and tumour thickness: challenges of early diagnosis. Arch Dermatol 1999;135:269–74.
16. Warycha MA, Christos PJ, Mazumdar M, et al. Changes in the presentation of nodular and superficial spreading melanoma over 35 years. Cancer 2008;113:3341–48.
17. Moloney FJ, Menzies SW. Key points in the dermoscopic diagnosis of hypomelanotic melanoma and nodular melanoma. J Dermatol 2011;38:10–15.
18. Bono A, Maurichi A, Moglia D, et al. Clinical and dermatoscopic diagnosis of early amelanotic melanoma. Melanoma Res 2001;11:491–94.
19. Bafounta ML, Beauchet A, Chagnon S, Saiag P. Ultrasonography or palpation for detection of melanoma nodal invasion: a meta-analysis. Lancet Oncol 2004;5:673–80.
20. Kalkhoran S, Milne O, Zalaudek I, et al. Historical, clinical, and dermoscopic characteristics of thin nodular melanoma. Arch Dermatol 2010;146:311–18.
21. Roseeuw D. The invisible melanoma. J Eur Acad Dermatol Venereol 2001;15:506–07.

CASE 2

ALICE HAS AN ITCHY FACIAL RASH

Alice is 4 months old. She was breastfed for 6 weeks and then changed to infant formula. About a month ago, she started to develop an itchy rash on her face and her mum, Donna, wonders if she is allergic to cow's milk.

QUESTION 1

What should you do next?

QUESTION 2

What questions should you ask Donna?

FURTHER INFORMATION

You have treated Donna for asthma in the past but no one in the family has had trouble with eczema. However, further questioning revealed significant atopy in the family. Dad has hay fever and Donna's mum had migraines and asthma. A naturopath suggested soy formula and calendula ointment, and cautioned against the use of steroid creams.

QUESTION 3

What should your examination of Alice involve?

FURTHER INFORMATION

You have diagnosed atopic eczema. Examination revealed excoriated eczema of the cheeks with typical sparing of the peri-oral area. There were patches of eczema around the earlobes, in the cubital and popliteal fossae, and small patches on the body but not in the nappy area. The history was not suggestive of a milk allergy. Donna has tried the calendula and has just commenced a soy formula. She has also tried very small amounts of 0.5% hydrocortisone cream bought over-the-counter. Nothing much has helped and Donna is not coping well because Alice keeps waking up distressed.

QUESTION 4

What complications of eczema do you need to be aware of?

QUESTION 5

What treatment will you start?

FURTHER INFORMATION

Donna is not very keen on steroids. She has heard bad stories about side effects and the naturopath told her to avoid them.

QUESTION 6

Will she use the prescription you organised?

QUESTION 7

What follow-up will you organise?

CASE 2 ANSWERS

ANSWER 1

Options for a course of action might include changing the formula and seeing how she goes, examining her face and/or asking Donna questions about the rash.

The most important thing at this stage is to take a history. The history is important for both diagnosis and treatment, as it will help to engage Donna in a management plan, which is likely to be long term.

ANSWER 2

Questions that could be asked of Donna include the following.

- How itchy does Alice get? Is it a major feature?
- Is Alice's sleep disturbed?
- Is the family atopic? Ask about asthma, eczema and hayfever. You may already know this from previous family consultations. Urticaria (hives) is also an indication of atopy.
- What has Donna tried so far?
- Has Donna had advice from anyone (e.g. family members, pharmacist, child health nurse, naturopath)?
- What does Donna think has caused Alice's skin trouble?
- Does the rash flare up soon after a feed? Does the skin become urticarial or red if milk spills onto the face? These features are suggestive of allergy.

ANSWER 3

You should examine all of Alice's skin. Ask Donna to undress her while you are asking questions. Look at the nappy area as well; this is often not affected as the area is kept humid and protected by the nappy. Feel the skin as well; is it dry? Remember to check the scalp, ears, hands and feet. Is the skin excoriated? Are there any pustules?

ANSWER 4

Atopic eczema (also called atopic dermatitis), which is characterised by itching, is the most common chronic skin condition that affects youngsters. Typically it presents initially in the first 12 months of life.

In young children, sleep is often interrupted by itching, which is worsened by overheating in bed. This leads to overtiredness and worsening of daytime behaviour and routines, resulting in poor quality of life for the child and family.[1] Note, the words eczema and dermatitis can be used interchangeably as a distinction between the terms is not recognised medically.[1]

Secondary infection is common in eczema. Infection may be bacterial, viral or fungal in nature.[2] There may be pustules or blisters (impetigo). Pustules in crease areas may be due to thrush. The most common cause of secondary infection is *Staphylococcus aureus*,[1,3] and a low grade infection may not be obvious.

Treatment of secondary infection may be warranted using an antiseptic product in the bathwater or topically on the skin.[1] Oral antibiotics could also be considered to manage a bacterial secondary infection or where bacterial infection is suspected and the skin has not improved using other approaches.[1,3] Management of other infections (viral or fungal) may also need to be considered.

Extensive erythrodermic eczema may cause significant fluid and heat loss and lead to hypothermia, dehydration and shock. Chronic severe eczema may produce growth retardation.[4] These complications are associated with very severe disease and are not commonly seen in general practice.

ANSWER 5

A number of aspects will need to be considered in developing a treatment plan.[5] These include the following points.

- **An explanation of atopic eczema:** many parents think that the eczema is caused by an allergy and that avoidance of the allergen will cure the eczema. Explain that Alice has been born with a genetic predisposition to sensitive skin that is prone to dryness and itch. Her skin is more prone to irritation and she will require regular treatment with moisturisers.
- **Prescribe a topical steroid:**[1] topical steroids are generally the most effective topical treatment for eczema. They usually work quickly to reduce itch and inflammation. Ointments are more effective and do not usually sting when applied to broken skin, in contrast to creams. However, they are messier and once the worst of the eczema has settled, a change may be made to a cream. Current guidelines recommend the use of hydrocortisone (1%)[1,3] or desonide as first-line treatment for the face[1] and use of a stronger topical steroid if unresponsive.[1,3] Once daily application of a topical steroid is recommended. Application after a bath is often the most practical time. More frequent application of corticosteroids above that recommended in guidelines does not provide additional benefits.[3]
- **Protect the skin:** use a moisturiser at every nappy change and all over the skin after bathing. A bath oil can be added to the bath or soap substitute used for washing.[3] If the skin is broken, an ointment will be more soothing. Options include liquid paraffin mixture or emulsifying ointment.
- **Avoid skin irritants:** this includes excessive heat (especially when sleeping), coarse fabrics, wool next to the skin, soap, fabric softeners and sandpits.[1]
- **Provide patient information:** provide written information on eczema and the use of topical steroids[6] (see Resources section below). It may be worth providing contact details for the Eczema Association.

Lastly, there is a lack of high-quality evidence to support the use of probiotics and complementary therapies, such as evening primrose oil, in the management of atopic eczema.[2]

ANSWER 6

In atopic eczema poor compliance to therapy often leads to treatment failure.[1]

It is very important to discuss the use of topical steroids otherwise they may be used too sparingly or not at all. Explain the vast difference between topical and oral steroids, and that studies have shown very little risk of skin thinning or systemic side effects when used appropriately.[7,8,9]

Explain to Donna that the pharmacist will probably tell her to use the steroid sparingly, but that she may safely use the amounts you have indicated. Guidelines recommend noting the amount of cream to be applied on the prescription and underlining the information. This will ensure that the medication is labelled correctly at the time of dispensing and that the patient is counselled appropriately by the pharmacist.[1]

ANSWER 7

Follow-up in 2–3 weeks should be arranged to monitor progress and to allow more questions and explanations about eczema.[10]

Ensure there are enough quantities and repeats for the topical steroid to allow continued treatment. An infant with extensive eczema will require about 5 g of topical steroid a day, which would require an authority for 8 tubes of 15 g each per month.[11]

If there has not been a major improvement in the eczema, consider the possibilities of secondary infection or a significant allergy[11] or poor compliance. Check how much topical steroid has been used. It may be appropriate to do a skin swab, or organise a referral. Referral to a dermatologist is recommended if there are problems with the diagnosis, or if topical therapy does not control the eczema, or other therapies such as phototherapy or systematic agents are indicated, or in the case of recurrent secondary infections.

REFERENCES

1. Dermatology Expert Group. Therapeutic Guidelines: dermatology, version 3. In: eTG complete [Internet]. Melbourne. Therapeutic Guidelines Limited 2009.
2. Dermatological drugs: eczema. In: Australian Medicines Handbook 2013. Australian Medicines Handbook Pty Ltd; Adelaide.
3. New Zealand Dermatological Society. Atopic eczema. Available at www.dermnetnz.org/dermatitis/dermatitis.html [Accessed 7 January 2014].
4. Eichenfield LF, Tom WL, Chamlin SL, Feldman SR, Hanifin JM, Simpson EL, et al. Guidelines of care for the management of atopic dermatitis: J Am Acad Dermatol 2013;doi:10.1016/j.jaad.2013.10.010. Available at www.jaad.org/article/S0190-9622(13)01095-5/ [Accessed 7 January 2014].
5. Ross T, Ross G, Varigos G. Eczema – practical management issues. Aust Fam Physician 2005;34:319–24.
6. Long CC, Finlay AY. The finger-tip unit – a new practical measure. Clin Exp Dermatol 1991;16:444–47.
7. Lee M, Marks R. The role of corticosteroids in dermatology. Aust Prescriber 1998;21:9–11.
8. Berth-Jones J. Topical treatments used in the management of skin disease. In Burns T, Breathnach S, Cox N, Griffiths C (eds). Rook's Textbook of Dermatology – 8th ed. Oxford: Wiley-Blackwell; 2010; Vol 4. Chapter 73, p. 1–23..
9. Hong E, Smith S, Fischer G. Evaluation of the atrophogenic potential of topical corticosteroids in pediatric dermatology patients. Pediatr Dermatol 2011;28:393–96.

10. Hanifin JM, Cooper KD, Vincent CH, Kang S, Krafchik BR, Margolis DJ, et al. Guidelines of care for atopic dermatitis. J AmAcad Dermatol 2004;50:391–404.
11. Newland K, Warren L, Gold M. Food allergy testing in infantile eczema: a clinical approach and algorithm. Aust J Dermatol 2013;54:79–84.

RESOURCES FOR PATIENTS AND DOCTORS

- Eczema Association of Australasia www.eczema.org.au
- New Zealand Dermatological Society www.dermnetnz.org
- National Eczema Society (UK) www.eczema.org
- Patient leaflet: Topical steroids – how much do I use? Australian Medicines handbook. Last updated May 2012 (includes data for application of steroids in infants and children. Available at www.amh.net.au/downloads/fingertipunits.pdf
- Patient leaflet: Eczema. Australasian Society of Clinical Immunology and Allergy (last updated April 2010). Available at www.allergy.org.au/patients/skin-allergy/eczema
- Patient leaflet: Eczema. Asthma Australia. Available at www.asthmaaustralia.org.au/Eczema.aspx

CASE 3

DARREN IS HAVING PROBLEMS WITH A RASH ON HIS HANDS

Over the last 6 months or so, Darren has been developing red, scaly, itchy patches on the back of his hands. It seemed to start after a change in the handwash at work and his mother thought it might have been a reaction to the product.

Darren is 25 years of age and works in retail in an IT store. He is becoming embarrassed about the rash on his hands. Some customers seem to try to avoid him.

QUESTION 1

Is this contact dermatitis?

FURTHER INFORMATION

Itch is not a major feature of his rash. He has tried his mum's cortisone cream with slight improvement. Darren has had scaly patches on his elbows and knees since he was about 17 years old. However, in the last year or so he has developed more and more patches on his body, scalp and now the back of his hands. He smokes 15 cigarettes a day and has a few drinks at the weekends.

QUESTION 2

What questions should you ask?

QUESTION 3

How would you examine Darren?

FURTHER INFORMATION

You have confidently diagnosed chronic plaque psoriasis; the new patches on his hands are plaques of psoriasis.
History and examination will usually facilitate a diagnosis of psoriasis for most patients. Depending on the presentation differential diagnosis includes:

- eczema: usually itchier and does not have the thick scale seen with psoriasis
- fungal infection(s): consider taking scrapings for culture if diagnosis is not clear
- skin tumours: organise biopsy and/or referral if in doubt; caution is recommend in the case of isolated plaques (psoriasis is usually symmetrical) that grow despite treatment
- seborrhoeic dermatitis: appearance may be similar to psoriasis.[1]

QUESTION 4

Why is the hand rash not contact dermatitis?

QUESTION 5

Now that you have diagnosed psoriasis, are there any other specific questions you want to ask Darren?

QUESTION 6

What treatment will you organise?

FURTHER INFORMATION

Psoriasis is an autoimmune inflammatory disease involving the skin, joints and cardiovascular system. Psoriasis is associated with an increased risk of cardiovascular disease, obesity, diabetes and depression.[2] It is important to assess all of the patient's risk factors and to address these as part of the overall treatment plan. It is important that the patient appreciates this. It may be a powerful motivator to address major issues such as smoking and obesity.[3] Psoriasis is not just a rash.

QUESTION 7

Is there a need for any investigations?

QUESTION 8

Is there a need for long-term follow-up even if the psoriasis is under control?

CASE 3 ANSWERS

ANSWER 1

This could be contact dermatitis; however, as hand rashes can be easily misdiagnosed it is important to take a careful history and undertake an examination before forming a diagnosis.

ANSWER 2

Appropriate questions to ask Darren include the following.

- Is the rash itchy?
- What treatments has he tried?
- Does he have any other rashes?
- Does he drink or smoke?
- Is there a family history of rashes or arthritis?
- Did the rash coincide with an illness or extra stress?
- Does he have a history of eczema/dermatitis or atopy?
- Does he take any medication(s)? Drug-induced skin reactions are adverse effects of some medications. For example, lithium, beta-blockers, antimalarials and nonsteroidal anti-inflammatory drugs may precipitate or exacerbate psoriasis.[4,5,6]

ANSWER 3

You certainly need to examine Darren's hands carefully but it is important to check all of Darren's skin. Remember to check his nails, ears, scalp and crease areas such as the natal cleft and umbilicus.

ANSWER 4

It is sometimes very difficult to differentiate between dermatitis and psoriasis of the hands. Generally, dermatitis is itchier and may show major improvement with time away from work. The patches tend to be less well defined than psoriasis, and often involve the more delicate skin in the finger webs and around the wrists. People with contact dermatitis are also more likely to be atopic.[7]

Plaque psoriasis may appear anywhere on the body but commonly affected areas include the elbows, knees, lower back (sacrum) and scalp.[4,5,6] Flat areas of psoriasis are referred to as plaques and these are usually well delineated and pink with a silvery scale. There may be single or numerous lesions. Individual plaques may join to form extensive areas of 30 cm or more in diameter.[4,5,6]

ANSWER 5

An association has been noted between psoriasis and the development of joint pain. About one in three people with psoriasis may develop associated mild-to-severe arthritis (psoriatic arthritis).[4] The symptoms of psoriatic arthritis are transitory but the condition is life-long and can eventually result in significant damage to joints. Severe disease may result in a shorter life expectancy.[5,6] It is important therefore to ask Darren questions such as those suggested below.

- Does Darren have any problems with painful joints?
- Does he have early morning stiffness in the joints?
- Has he had swelling of individual fingers or toes (dactylitis)?
- Has he had sore Achilles or elbows, or pain in the arch of the foot when first standing up in the morning (enthesopathy)?
- Does Darren have any other symptoms or features that have been associated with psoriatic arthritis? These may include fatigue, eye inflammation (iritis), mouth ulcers and nail changes. Examination of Darren's hands may reveal thickening and subungual hyperkeratosis and/or separation of the nail from the nail bed (onycholysis) or nail pitting (psoriatic nail dystrophy).

ANSWER 6

Small areas of thin psoriasis usually respond well to topical steroid.[8] The type and potency of the corticosteroid chosen should be guided by the severity and site of the psorisias, as well as the age of the patient.[9] For Darren, you could start with a reasonably potent topical steroid such as mometasone. Ointments are more efficient and more moisturising but are messier. A cream may be used once the worst of the psoriasis has settled. Intermittent use of a combined steroid/calcipotriol ointment works well for some patients.

Darren may be happy to concentrate on clearing the hand lesions, but long-term control of the rest of his psoriasis will probably entail systemic treatment. Options include ultraviolet light therapy, methotrexate or acitretin.[4,9,10,11]

A referral to a dermatologist or another specialist (e.g. rheumatologist) may be required. Referral may be considered in the following cases:[1,9,12]

- diagnostic uncertainty
- the psoriasis not being well controlled
- the psoriasis being severe or extensive, or progressing rapidly
- the psoriasis cannot be controlled by topical therapy
- co-existing arthropathy is significant
- there is erythrodermic or pustular psoriasis, as these forms of psoriasis can lead to severe systemic illness.

ANSWER 7

As psoriasis has been associated with a number of conditions that may impact on mortality and morbidity, such as cardiovascular disease, diabetes, renal disease and rheumatological disease,[12,13] other comorbidities and risk factors need to be addressed. It would be appropriate to check the following, particularly if treatment with a systemic agent is being considered:

- full blood count (FBC)
- creatinine and electrolytes (C&E)
- liver function test (LFT)
- urinalysis
- fasting blood sugar levels (BSL) and lipids
- blood pressure
- weight and BMI.

As psoriasis can be aggravated by stress, discussion about stress management techniques and exercise, as well smoking cessation and reduction of alcohol intake, may be warranted.[4]

Preventive advice, including lifestyle advice, provision of behaviour change information and overall support should also be provided, depending on an individual's situation.[12,14]

ANSWER 8

Darren should be reviewed about every 6 months, even if the psoriasis is well controlled.[2]

It is important to assess the psychological and social wellbeing[15] of patients with psoriasis and, where feasible, to manage problems or alternatively to refer patients to appropriately qualified individuals. It is important to monitor Darren's risk factors for cardiovascular disease, diabetes and depression.

REFERENCES

1. Clarke P. Psoriasis. Aust Fam Physician 2011;40:468–73.
2. Gunther L, Gulliver W. Psoriasis comorbidities. J Cutaneous Med Surg 2009;13:S77–S87.
3. Butler CC, Rollnick S, Cohen D, et al. Motivational consulting versus brief advice for smokers in general practice: a randomised trial. Br J Gen Pract 1999;49:611–16.
4. Dermatology Expert Group. Therapeutic Guidelines Dermatology, version 3, In: eTG complete [Internet]. Melbourne. Therapeutic Guidelines Limited 2009. Available at www.tg.org.au/complete [Accessed 7 January 2014].
5. New Zealand Dermatological Society. Psoriasis. Available at www.dermnetnz.org/scaly/psoriasis-general.html [Accessed 7 January 2014].
6. New Zealand Dermatological Society. Plaque psoriasis. Available at www.dermnetnz.org/scaly/plaque-psoriasis.html [Accessed 7 January 2014].
7. Belsito DV, Occupational contact dermatitis: etiology, prevalence, and resultant impairment/disability. J Am Acad Dermatol 2005;53:303–13.
8. Mason J, Mason AR, Cork MJ. Topical preparations for the treatment of psoriasis. Br J Dermatol 2002;146:351–64.
9. Australian Medicines Handbook Psoriasis. Adelaide. Australian Medicines Handbook Pty Ltd 2013.
10. Pathirana D, Ormerod AD, Saiag P, et al. European S3-guidelines on the systemic treatment of psoriasis vulgaris. J Eur Acad Dermatol Venereol 2009;235–70.
11. Baker C et al Treatment goals for moderate to severe psoriasis: An Australian consensus. Aust J. Derm 2013; 54:148–54.
12. National Institute for Health and Care Excellence. Psoriasis: the assessment and management of psoriasis. NICE Clinical Guideline 153. London. Available at www.nice.org.uk/CG153 [Accessed 7 January 2014].
13. Yeung H, Takeshita J, Mehta NN. Psoriasis severity and the prevalence of major medical Comorbidity: a population-based study. JAMA Dermatol 2013;149:1173–79.
14. The Royal Australasian College of General Practice. Guidelines for preventive activities in general practice. 8th Edn. East Melbourne 2012. Available at www.racgp.org.au/your-practice/guidelines/redbook [Accessed 24 January 2014].
15. Margin PJ, Adams J, Heading GS, Pond DC. Patients with skin disease and their relationships with their doctors: a qualitative study of patients with acne, psoriasis and eczema. Med J Aust 2009;190:62–64.

RESOURCES FOR PATIENTS AND DOCTORS

- Australasian College of Dermatology. A–Z of skin: psoriasis. Available at www.dermcoll.asn.au/public/a-z_of_skin-psoriasis.asp
- Psoriasis Australia. Available at www.psoriasisaustralia.org.au/
- Better Health Channel. Psoriasis. Available at www.betterhealth.vic.gov.au/bhcv2/bhcarticles.nsf/pages/Psoriasis_explained
- Arthritis Australia. Arthritis information sheet: psoriatic arthritis. Available at www.arthritisaustralia.com.au/images/stories/documents/info_sheets/2013/PsoriaticArthritis.pdf
- PsoriasisNet: A comprehensive online psoriasis information resources (US). Available at www.skincarephysicians.com/psoriasisnet/
- Psoriasisguide.com
- Mayo Clinic USA. Psoriasis. Available at www.mayoclinic.org/diseases-conditions/psoriasis/basics/definition/CON-20030838
- My Skin's on Fire. Available at www.youtube.com/watch?v=kQID72UXNUI
- British Association of Dermatologists. Psoriasis – an overview. Available at www.bad.org.uk/site/864/Default.aspx

CASE 4

JULIE'S STRANGE NAILS

Julie, aged 59 years, is semi-retired. She presents complaining of problems with her toenails. She usually keeps her toenails polished and noticed at a recent pedicure that the nails on her big toes were developing white patches. She reports no pain. Julie is generally well apart from occasional back pain. She takes no regular medications.

On examination, you notice a yellow-white opaque streak across one side of her left toe. Her right toe has extensive streaking, some thickening and there is evidence of separation and lifting of the toenail from the nailbed at the tip of the nail, progressing back. The border between the pink, healthy portion of the nail and the area where the nail appears to have lifted is irregular and fuzzy. It seemed to get worse after she had a pedicure whilst on holiday.

QUESTION 1

What is the most likely diagnosis?

QUESTION 2

Would you undertake any investigations?

FURTHER INFORMATION

You advise Julie that she has what seems to be a fungal nail infection and that you need to obtain laboratory confirmation of your diagnosis before you can discuss treatment options. You collect nail samples to send off for microscopy and culture and advise Julie that final microscopy and culture may not be completed for up to 1 month. You ask her to make a follow-up appointment to see you when her results are available.

As Julie gets up to leave, she recalls that her husband, who recently completed his last session of chemotherapy, had been taking an oral antifungal agent. She cannot recall the name of the medication. You realise that Julie is referring to the ketoconazole tablets prescribed for her husband's oropharyngeal candidiasis. She asks you if she should she start taking any leftover tablets to help her nails along?

QUESTION 3

What would you say to Julie about taking her husband's ketoconazole tablets?

FURTHER INFORMATION

Julie returns to see you when the laboratory results are available. Histology and cultures may be negative in 10–30% of cases and a negative test does not exclude onychomycosis. Multiple organisms may cause onychomycosis. Laboratory tests may include potassium hydroxide (KOH) staining to detect fungal dermatophytes, or confirmation by histology or culture[8]. Julie's laboratory results state: 'Fungal elements seen: trichophitum species'.

Julie has been reading about nail infections on the internet and is keen to discuss treatment options, especially a new laser nail therapy technique she has read about.

QUESTION 4

Briefly, what management options would you recommend?

QUESTION 5

What advice would you give about topical therapy?

QUESTION 6

Which oral medications would you consider and if so, at which doses?

QUESTION 7

What would you tell Julie about the risk and benefits of oral therapy?

FURTHER INFORMATION

Julie would prefer a less invasive management option with a quick turnaround time. She likes what she has read about laser nail therapy and would like to try it. She asks you for your opinion.

QUESTION 8

What would you say to her about laser nail therapy?

CASE 4 ANSWERS

ANSWER 1

This seems to be a fungal nail infection (onychomycosis). Although not life-threatening, onychomycosis may cause pain, discomfort and disfigurement, which may lead to physical limitations. Toenail infections occur more often than fingernail infections.[1] Organisms associated with onychomycosis include dermatophytes (e.g. *Trichophyton rubrum (T rubrum), T. interdigitale* – the infection is also known as tinea unguium), yeasts (e.g. *Candida albicans*) and moulds (e.g. *Scopulariopsis brevicaulis*, *Fusarium*).[2]

There also appears to be oncholysis, which is the separation of a nail from the nail bed, in the right toenail. Oncholysis most often starts at the tip of the nail and progresses back. It is often caused by repetitive trauma, aggressive manicure technique or extended immersion of nails in water. Oncholysis may also be caused by infection or medications (e.g. tetracyclines, fluoroquinolone antibiotics, chlorpromazine, oral contraceptives and some anti-cancer treatments). It is infrequently associated with underlying disease (e.g. multiple myeloma, anaemia, diabetes, erythropoietic porphyria, hyperthyroidism, hypothyroidism, impaired peripheral circulation, Reiter syndrome, sarcoidosis, scleroderma, yellow nail syndrome due to chronic lung, or sinus disease).[3]

Differential diagnosis [2,4] includes consideration of:

- bacterial infection, especially *Pseudomonas aeruginosa*, which turns the nail black or green
- psoriasis, eczema and/or dermatitis
- lichen planus
- viral warts
- onychogryphosis (nail thickening and scaling under the nail), common in the elderly
- melanoma.

ANSWER 2

Before commencing treatment it is important to definitively establish a diagnosis microbiologically. The reasons for this are manifold:[1,5]

- other nail problems can mimic tinea
- antifungal treatment will not be successful if the problem(s) is due to other causes
- identification of the responsible organism is important as microscopy/culture results may influence treatment choices
- prior treatment reduces the chance of growing fungus and partially treated infection may be impossible to prove for many months as antifungal drugs can be detected even a year later
- treatment is often over a prolonged period of time and is expensive.

Current recommendations suggest taking clippings of the affected nail, including scrapings from the discoloured surface of the nail, and debris from under the nail where feasible.[1, 5] Microscopy and culture are positive in about 80% of onychomycosis cases.[1]

ANSWER 3

This question provides the clinician with an opportunity to highlight important medication safety points: 1) the importance of not sharing medications prescribed for others and the possible risks associated with such practices; and 2) the importance of taking medications prescribed specifically for the patient by a health professional, which minimises the possible harms of over or under treatment.

You explain to Julie that she must not use ketoconazole tablets for her nail infection. You explain the basic principles stated above and reaffirm the importance of obtaining laboratory confirmation of your tentative diagnosis. You also advise that her fungal infection is different from the infection that her husband was being treated for.

Lastly, on 1 December 2013, the Therapeutic Goods Admiration (TGA) in consultation with the manufacturers of ketoconazole decided to deregister and discontinue the oral formulation of ketoconazole in Australia, because of concerns regarding serious liver toxicity.[6,7] Topical preparations will continue to be available (cream and shampoo). You advise Julie not to use any remaining tablets under any circumstances and to take any remaining medication to her local pharmacy for safe disposal.

ANSWER 4

A number of management options could be considered. Combining topical and systemic treatments increases the possibility of treating the fungal infection. In some severe cases, surgical toenail removal and debridement may also be required, but almost always in combination with oral and other treatments.[9]

Three options could be considered. These include topical therapy, oral therapy and/or non-pharmacological approaches, for example laser treatment, photodynamic therapy, mechanical, chemical or surgical nail avulsion; chemical removal of the nail with a 40–50% urea compound in patients with very thick nails; or removal of the nail plate as an adjunct to oral therapy. The lesions should be treated as there is potential for further fungal infections at distant sites, or complications relating to the infections, particularly in the elderly, patients with diabetes and patients who are immunocompromised.[10]

ANSWER 5

Topical therapy is associated with a low success rate and high recurrence rate, despite prolonged therapy.[11] Topical therapy is usually combined with oral therapy, which increases success rates,[12] but adds to the cost and potential for side effects. The duration of treatment is in excess of 6 months. Topical therapy alone is only viable for superficial, distal nail infection[1] or mild infections.[10] It is also important to advise patients that while nail infections can be cured, it may take considerable time for the nail(s) to grow out and resume a healthy appearance.[13] It may take up to 9 months for substantial nail dystrophy to grow out.[1] It is also important to advise patients against the use of topical preparations available over

the internet, as the composition and efficacy of such products is uncertain.

ANSWER 6

Current guidelines recommend the use of terbinafine as first-line treatment, prescribed at 250 mg daily for 12 weeks (or longer) for toenails.[1,13] If terbinafine is not tolerated, itraconazole or fluconazole could be considered.[1] Substantially longer treatment is required with fluconazole for toenails.[1] In renal impairment (creatinine clearance less than <50 mL/min, including dialysis) the dose of terbinafine should be reduced to 125 mg daily.[13]

Before commencing therapy, baseline liver function tests should be performed, and liver function and blood count should be monitored where planned treatment will be longer than 6 weeks.[13] Therapy should be ceased if liver toxicity arises.

Interactions between antifungal agents and warfarin have been reported. While both increases and decreases in prothrombin time have been reported in patients using terbinafine and warfarin concomitantly,[1,14] a causal relationship has not been demonstrated.[15] Azole antifungal agents, which include fluconazole, itraconazole and ketoconazole, may reduce warfarin metabolism, increasing its anticoagulant effect and leading to bleeding.[13] Griseofulvin has been reported to reduce the anticoagulant effects of warfarin.[13] Management of potential interactions may require additional INR monitoring and/or warfarin dose changes.[13]

Remember that ketoconazole, the use of which was previously limited by severe liver complications,[1] has been removed from the market because of the risk of liver toxicity, as discussed earlier.

ANSWER 7

A cure rate of 70–80% has been described for terbinafine, whereas itraconazole and fluconazole have cure rates of around 60–70%. In a post-marketing survey of more than 25 000 patients, the incidence of adverse events was 10.5%, mostly gastrointestinal and skin reactions, which were typically mild in nature. There was a low risk of serious adverse events (0.04%).[17]

Griseofulvin is considered safe but is less effective and relapse is common. It can also cause nausea and has a cure rate of about 30% after prolonged continuous therapy (i.e. 12 months or more).[1] For these reasons many patients choose not to use griseofulvin.

ANSWER 8

Laser therapy is a relatively new therapy for the treatment of nail fungal infections, but all infectious agents can be treated with heat,[18] which is the basis of laser therapy. It is well tolerated and has been shown to be very effective and to have high cure rates in a limited number of studies.[19,20] Typically requiring two or more treatment sessions, which can be combined with podiatric debridement, the therapy may be considered minimally invasive and avoids potential side effects from drug therapy.[21] It is also a cost-effective treatment, as prolonged treatment with oral and topical agents is expensive, particularly as there is a high failure rate and requirement for additional therapy. Although these initial promising findings need to be confirmed in a randomised trial,[4] the few treatments required, high patient acceptability and avoidance of systemic antifungal drugs makes it appealing as a first-line therapy for this common disease. *Figures 1* and *2* show images of a nail before and after laser therapy.

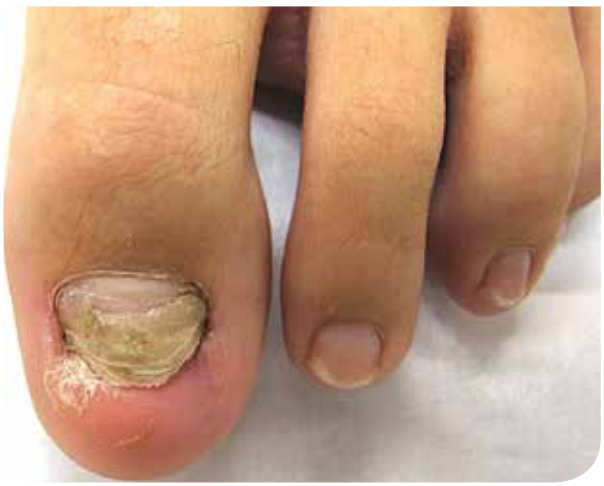

Figure 1. Nail before treatment; the left big toenail shows extensive onychomycosis

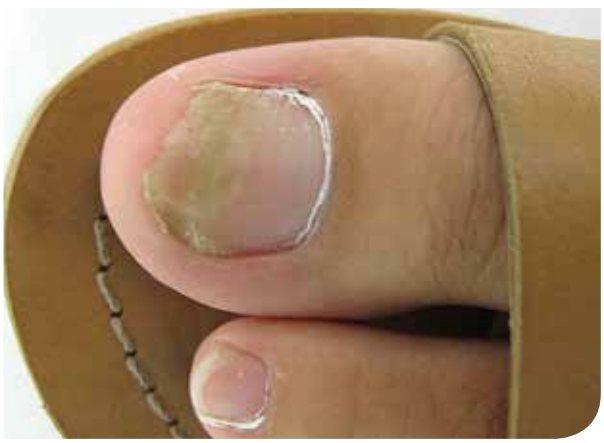

Figure 2. Nail after treatment; the toenail is shown after two treatments 1 month apart

Patients should be advised to seek qualified laser therapists and high quality equipment, as not all laser is suitable, nor are all therapists qualified or expert in this treatment. Several lasers have been approved by regulatory agencies such as the FDA. These include the YAG continuous, short or long pulsed lasers, the diode laser and the Ti:Saphire modelocked laser.[2] Failure of laser therapy could be in part due to poor equipment and inadequately trained therapists.

REFERENCES

1. Tinea of the nails (onychomycosis, tinea unguium). In: eTG Complete [Internet]. Melbourne: Therapeutic Guidelines Ltd; 2013. Available at www.tg.org.au [Accessed 25 November 2013].
2. Fungal nail infections (onchymycosis). DermNetNZ [last updated 29 April 2013]. Available at www.dermnetnz.org/fungal/onychomycosis.html [Accessed 25 November 2013].

3. DermNetNZ. Onycholysis [last updated 2 November 2012]. Available at www.dermnetnz.org/hair-nails-sweat/onycholysis.html [Accessed 25 November 2013].
4. DermNetNZ. Melanoma of nail unit [last updated 18 August 2012]. Available at www.dermnetnz.org/fungal/fungi-laboratory.html [Accessed 25 November 2013].
5. DermNetNZ. Laboratory tests for fungal nail infection [last updated 11 September 2012]. Available at www.dermnetnz.org/fungal/fungi-laboratory.html [Accessed 25 November 2013].
6. NPS Medicinewise. Ketoconazole discontinued. Available at www.nps.org.au/health-professionals/health-news-evidence/2013/ketaconazole-discontinued [Accessed 19 November 2013].
7. Australian Government Department of Health Therapeutic Goods Administration. Oral ketoconazole (Nizoral) 200 mg tablets product deregistration (10 October 2013). Available at www.tga.gov.au/safety/alerts-medicine-oral-ketoconazole-131010.htm [Accessed 25 November 2013].
8. Rodgers P, Bassler M. Treating onychomycosis. Am Fam Physician 2001;63:663–72, 77–78.
9. Cohen PR, Scher RK. Topical and surgical treatment of onychomycosis. J Am Acad Dermatol 1994;31:S74–77.
10. Thomas J, Jacobson GA, Narkowicz CK, Peterson GM, Burnet H, Sharpe C. Toenail onychomycosis: an important global disease burden. J Clin Pharm Ther 2010;35:497–519.
11. Gupta AK, Simpson FC. New therapeutic options for onychomycosis. Expert Opin Pharmacother 2012;13:1131–42.
12. Gupta AK, Paquet M. Improved efficacy in onychomycosis therapy. Clin Dermatol 2013;31:555–63.
13. Rossi S, editor. Australian Medicines Handbook 2013. Adelaide: Australian Medicines Handbook Pty Ltd. 2013.
14. Warwick JA. Corrall RJ. Serious interaction between warfarin and oral terbinafine. BMJ 1998;316:440.
15. Highlights of prescribing information (last revised 10/2013). Available at www.pharma.us.novartis.com/product/pi/pdf/Lamisil_tablets.pdf [Accessed 16 December 2013].
16. Casciano J, Amaya K, Doyle J, et al. Economic analysis of oral and topical therapies for onychomycosis of the toenails and fingernails. Manag Care 2003;12:47–54.
17. Hall M, Monka C, Krupp P, O'Sullivan D. Safety of oral terbinafine: results of a postmarketing surveillance study in 25,884 patients. Arch Dermatol 1997;133:1213–19.
18. Tchernev G, Penev PK, Nenoff P, et al. Onychomycosis: modern diagnostic and treatment approaches. Wien Med Wochenschr 2013;163:1–12.
19. Waibel J, Wulkan AJ, Rudnick A. Prospective efficacy and safety evaluation of laser treatments with real-time temperature feedback for fungal onychomycosis. J Drugs Dermatol 2013;12:1237–42.
20. Kimura U, Takeuchi K, Kinoshita A, Takamori K, Hiruma M, Suga Y. Treating onychomycoses of the toenail: clinical efficacy of the sub-millisecond 1,064 nm Nd: YAG laser using a 5 mm spot diameter. J Drugs Dermatol 2012;11:496–504.
21. Ledon JA, Savas J, Franca K, Chacon A, Nouri K. Laser and light therapy for onychomycosis: a systematic review. Lasers Med Sci 2012;27:10.1007/s10103-012-1232-y.

RESOURCES FOR DOCTORS AND PATIENTS

- Better Health Channel. Nails – fingernail and toenail problems [last reviewed September 2013]. Available at www.betterhealth.vic.gov.au/bhcv2/bhcarticles.nsf/pages/Nails_-_fingernail_and_toenail_problems

CASE 5

DALE'S UNCOMFORTABLE FOOT LESIONS

Dale, aged 17 years, is a keen footballer who over the last 12 months has developed uncomfortable skin lesions on the dorsum and plantar aspects of his feet, which he initially thought were calluses from his football boots. They have continued to grow and now the ones on the plantar aspect of his feet are uncomfortable. Dale is otherwise well, a non-smoker and no one else in his family has these lesions.

On examination there are extensive cauliflower-like lesions on the plantar and dorsal aspect of his feet (*Figures 1, 2*). Last weekend he played in a football final, which resulted in irritation to the dorsum of his foot. The rest of the skin on his feet appears normal, as do the nails.

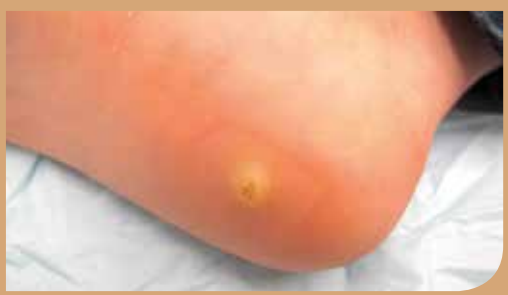

Figure 1. Plantar wart on the heel

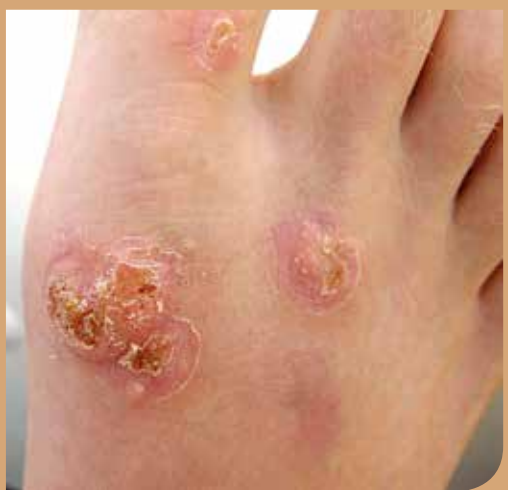

Figure 2. Warts on the dorsum of the foot

QUESTION 1

What is the most likely diagnosis?

QUESTION 2

Would you undertake any investigation?

FURTHER INFORMATION

Dale is told that he has warts. He recalls that many of his team members were told the same. He says that many of his friends had put duct tape on their warts and had used various home remedies such as thuja ointment.

QUESTION 3

What advice would you give Dale regarding treatment?

FURTHER INFORMATION

Dale returns after a month; he has tried the 35% salicylic acid gel, but with little improvement. The pharmacist advised 'take home' cryotherapy, but he wanted to speak to you before commencing this therapy, as he is frustrated that there has been little improvement in the condition.

QUESTION 4

What would you tell Dale about cryotherapy?

FURTHER INFORMATION

Dale says that he wants the lesions gone as soon as possible because the state trials are coming up.

QUESTION 5

What advice would you give about other therapies?

FURTHER INFORMATION

After extensive discussion, Dale is keen to proceed with laser therapy.

QUESTION 6

What would you tell Dale about laser therapy?

QUESTION 7

Dale has also been told that the warts are contagious. What is your advice?

FURTHER INFORMATION

After one month Dale returns after his first laser treatment (*Figures 3, 4*).

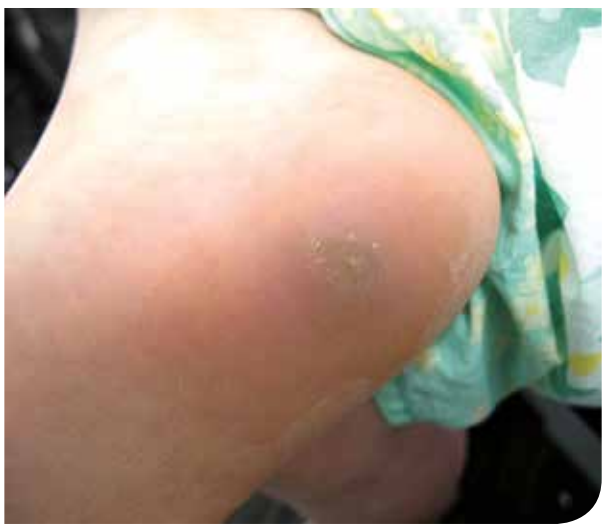

Figure 3. Treated plantar wart one month after laser therapy

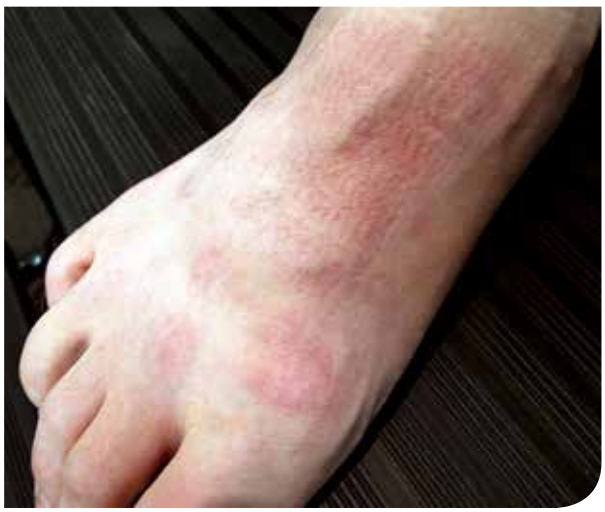

Figure 4. Treated warts one month after laser therapy

QUESTION 8

Dale asks about the long-term success of laser therapy, and if there is anything else he can do. How would you respond?

CASE 5 ANSWERS

ANSWER 1

The most likely diagnosis is warts. These occur relatively commonly on all skin surfaces and are caused by the human papillomavirus (HPV), of which there are many subtypes.[1]

Many infections are self-limiting, but where there is a warm, moist environment, such as the foot, they can thrive. Pain on weight-bearing aspects of the feet is not uncommon.

Warts on the feet are generally considered to be caused by different viruses from those causing genital warts, which most often involve HPV 6 and 11 subtypes,[2] although in the clinical situation the lesions are not biopsied or cultured. Plantar warts (verruca valgaris) involve HPV subtypes 1–4, 27, 29 and 57. While common warts (verucca vulgaris) involve HPV subtypes 1–5, 7, 27 and 29, appear most often on the hands and account for around 70% of non-genital warts.[3]

The differential diagnosis of any raised lesion includes solar keratosis, squamous cell carcinoma, basal cell carcinoma and embedded foreign body.[1,4] Cancerous conditions would be uncommon in a patient of Dale's age. In immunosuppressed patients the skin lesions may become extensive and may impair walking. Lesions may have been present for many years.

ANSWER 2

Plantar warts have a characteristic appearance and clinical examination usually identifies the wart(s). Note that in the case of benign warts, knowledge of HPV subtype will not influence choice of therapy.[4]

ANSWER 3

Guidelines suggest that indications for treatment of warts include pain, interference with function, cosmetic embarrassment and risk of malignancy. Treatments have a moderate success rate and warts may recur.[4] Treatment of warts is based on destruction of local tissue or immune modification.[5]

You advise Dale that home-based treatments may be worth trying for a few weeks. The key factor involved for successful treatment seems to be persistence. Skin care around the lesions is also important.

Recommended first-line treatment for common warts and plantar warts includes topical keratolytics (e.g. salicylic acid) or antivirals (podophyllum resin), with or without occlusion.[6] You mention that a commonly used over-the-counter remedy is salicylic acid; however, there is little information to enable comparison of different strengths and preparations containing salicylic acid.[4] Apart from its keratolytic actions, which result in destruction of the virus-infected epidermis, salicylic acid has weak antifungal and antibacterial properties.[5] It is also thought that the mild irritation resulting from treatment may stimulate an immune response in the patient.[4] Lastly, subgroup analysis data from a 2012 Cochrane publication exploring topical treatments for cutaneous non-genital warts in immunocompetent

adults and children, suggested that salicylic acid might be more efficacious for treating warts on hands than feet.[7]

Topical remedies must be applied daily to the lesions. It is important that the skin around the lesions is protected with nail polish applied to the skin.[6]

Caution should be taken when treating the feet of people with diabetes and/or peripheral vascular disease, as there is a risk of acute inflammation or ulceration.[5]

Duct tape occlusion, which is convenient and inexpensive, could be tried for 24 hours;[1] however there is limited evidence for success with this approach.[8]

Natural remedies include thuja ointment, which is also applied on a daily basis. Local allergy to thuja may be intolerable, and may be a reason for discontinuation

ANSWER 4

Where topical therapy has failed, cryotherapy may be used to freeze warts using liquid nitrogen as the cryogen of choice.[6]

Cryotherapy has been used with varying success rates. A 2011 study of 240 participants showed that 6-month clearance rates were similar for cryotherapy and salicylic acid (31% for salicylic acid versus 34% for cryotherapy) in the treatment of plantar warts.[9] Similarly, a 2012 meta-analysis failed to demonstrate significant differences in outcomes between cyrotherapy and salicylic acid across all wart sites, further affirming that cyrotherapy has similar success to salicylic acid treatment.[7]

The British Association of Dermatology recommends single or double freeze of warts for 15–20 seconds every 3–4 weeks.[4] This may need to be repeated several times, together with debridement of the wart between treatments.

In the author's experience, cryotherapy to the plantar area may be unsuccessful because of the pain involved in treating warts deeply embedded in the thick skin, which may require a higher amount of freezing. However, it may be useful as an interim measure while other treatments are being considered or while awaiting specialist consultation. Patients should be warned that cryotherapy produces pain and blistering[4] and, even if local anaesthetic were used for the freezing, walking may be difficult in subsequent days due to pain and swelling.

ANSWER 5

A number of other options, apart from occlusion and chemical topical treatments (e.g. salicylic acid) and cryotherapy, are available to treat warts. Additional treatment options include electrosurgery (curettage and cautery), topical or oral retinoids, fluorouracil cream, bleomycin injections, as well as immune-based treatment approaches, for example, imiquimod cream. Lastly, laser vaporisation or pulse dye laser destruction of feeding blood vessels could be considered.[1]

Note that specialist dermatological advice should be sought if intralesional bleomycin (a chemotherapeutic agent that inhibits DNA synthesis in viruses) or immunotherapy and cantharidin are considered.[6] Use of histamine H_2-receptor antagonists for the treatment of common warts is not currently recommended.[6]

In your surgery you are able to offer laser therapy and curetting of the wart.

ANSWER 6

Various lasers have been reported as being useful for the treatment of warts, with variable cure rates. For example, cure rates of 75–82% have been reported using CO_2 laser for treatment of common warts and pulsed dye laser (PDL) for treatment of extragenital and genital warts, respectively.[10] In a study of 369 patients using ND:YAG laser, an overall clearance rate of 96% was reported, with a 73% clearance following first treatment for verruca vulgaris.[11] ND:YAG laser has been shown to completely eliminate viral load (viral DNA) in treated warts, compared with untreated warts (100% viral DNA present) and cryo-treated warts (96% viral DNA present).[12] A recent study in 46 participants comparing two lasers reported that both PDL and ND:YAG lasers were effective in the management of resistant plantar warts, with no significant difference in cure rates or relapse rates. However, while PDL was safer and involved less pain, it required more treatments. ND:YAG was associated with greater pain and more complications, with haematoma being the most common.[13]

Laser treatment can be used together with curettage. Pain and discomfort are minimal. The light-based therapy works by cutting the blood supply to the wart. It may be administered as a series of 2–4 treatments at 4–6 weeks apart. Concomitant use of the immune modifier imiquimod may improve efficacy.[14,15] There is still some 'downtime' to enable treatment to be effective, but usually most sporting activities can be undertaken.

For optimal results, the upper layers or calloused skin must be minimised by paring with a medical blade. This allows for deeper penetration and more absorption by the targeted vascular component.

Patients usually state the laser feels 'like hot pulse or electric shock'; however, after laser application the lesion feels warm for the next few minutes. Disposable ice packs may be applied immediately after the laser application to decrease the heat. The desired appearance immediately after the pulse is a slight ashen colour.

It is recommended that the lesion is left uncovered after treatment to allow the heat to dissipate. The wart usually appears black or crusty within 24–72 hours of treatment and may remain like this for 1–2 weeks. Little black dots, which are blood vessels that have been heated, may also appear after laser. Treated tissue usually sloughs off 1–4 weeks after treatment. A blister may form if the heat temperature was too hot and if this occurs it must be treated as a wound. It is important not to laser outside the wart border. Mosaic warts are more resistant to therapy and may require multiple treatments or combination therapy with intralesional bleomysin.[16]

ANSWER 7

Transmission of warts is facilitated by direct and indirect means and occurs more often when skin is wet or damaged.[8] Infection may be transmitted from many locations, and clusters of infection may occur in families. HPV has spreads directly and sports changing room

showers or shared footwear are common sources of infection.[17] Guidelines recommend that patients are given information about reducing the risk of spreading infection.[5,8]

Dale is advised not to walk in bare feet, avoid sharing socks, shoes and towels with others, keep feet dry and change socks daily, use an antiseptic spray, and avoid scratching the lesions.[8]

ANSWER 8

Laser is a relatively new modality and there is paucity of data regarding long-term outcomes. In most cases, clinical clearance occurs after 2–3 treatments.[14] Failure of treatment may be due to a number of factors, training in use of the machine being uppermost. Immunosuppression, patient compliance and age-related healing can all impact on success.[4] Wart eradication may take longer in some individuals due to the large volume of the lesion.[14]

REFERENCES

1. DermNet NZ. Viral warts (last updated 23 June 2013). Available at www.dermnetnz.org/viral/viral-warts.html [Accessed 6 January 2014].
2. DermNet NZ. Genital warts (last updated 29 December 2013). Available at www.dermnetnz.org/viral/viral-warts.html [Accessed 6 January 2014]
3. Mulhem S, Pinelis S. Treatment of nongenital cutaneous warts. Am Fam Physician 2011;88:288–93.
4. Stirling JC, Handfield-Jones S, Hudson PM. Guidelines for the management of cutaneous warts. Brit J Derm 2001;144:4–11.
5. Salicylic acid. In: Australian Medicines Handbook 2013. Australian Medicines Handbook Pty Ltd; Adelaide. [Accessed 18 December 2013].
6. Human papillomavirus (revised February 2009). In: eTG Complete [Internet]. Melbourne: Therapeutic Guidelines Ltd; 2013. Available at www.tg.org.au [Accessed 18 December 2013].
7. Gibbs S, Harvey I. Topical treatments for cutaneous warts. Cochrane Database of Systematic Reviews 2006, Issue 3. Art. No.: CD001781. DOI: 10.1002/14651858.CD001781.pub2.
8. National Institute for Health and Care Excellence. Warts and verrucae. Available at cks.nice.org.uk/warts-and-verrucae [Accessed 11 January 2014].
9. Cockayne S, Hewitt C, Hicks K, et al. Cryotherapy versus salicylic acid for the treatment of plantar warts (verrucae): a randomised controlled trial. BMJ 2011;342:d3271.
10. Ockenfels HM, Hammes S. Laser treatment of warts. Hautarzt 2008;59:116–23.
11. Young Han T, Lee JH. Lee CK, et al. Long-Pulsed Nd:YAG Laser treatment of warts: report on a series of 369 cases. J Korean Med Sci 2009;24:889–93.
12. El-Tonsy MH, Anbar TE, El-Domyati M, Barakat M. Density of viral particles in pre and post Nd: YAG laser hyperthermia therapy and cryotherapy in plantar warts. Int J Dermatol 1999;38:393–98.
13. El-Mohamedy AE, Mearag I, El-Khalawny M, Elshahed A, Shokeir H, Mahmoud A. Pulsed dye laser versus Nd:YAG laser in the treatment of plantar warts: a comprehensive study. Laser Med Sci 2013; 10.1007/s10103-013-1479-y (Epub ahead of print).
14. Lipke MM. An armamentarium of wart treatments. Clin Med Res 2006; 4:273–93.
15. Hoyme UB, Hagedorn M, Schindler AE, et al. Effect of adjuvant imiquimod 5% cream on sustained clearance of anogenital warts following laser treatment. Infect Dis Obstet Gynecol 2002;10:79–88.
16. Dobson JS, Harland CC. Pulsed dye laser and intralesional bleomycin for the treatment of recalcitrant cutaneous warts. Lasers Surg Med 2013; doi: 10.1002/lsm.22199. [Epub ahead of print].
17. Rigo MV, Martinez-Campillo F, Verdu M, Cilleruelo S, Roda J. Risk factors linked to the transmission of papilloma virus in the school environment. Alicante, 1999. Aten Primaria 2003;31:415–20.

RESOURCES FOR PATIENTS AND DOCTORS

- Better Health Channel. Warts Fact sheet. Available at www.betterhealth.vic.gov.au/bhcv2/bhcarticles.nsf/pages/Warts
- Patient information for care of areas treated with liquid nitrogen. In: eTG Complete [Internet]. Melbourne: Therapeutic Guidelines Ltd; 2013. Available at www.tg.org.au

Dermatology

In order to qualify for 6 Category 2 points for the QI&CPD activity associated with this unit:

- read and complete the unit of *check* in hard copy or online at the *gplearning* website at http://gplearning.racgp.org.au
- log into the *gplearning* website at http://gplearning.racgp.org.au and answer the following 10 multiple choice questions (MCQs) online
- complete the online evaluation.

If you are not an RACGP member, please contact the *gplearning* helpdesk on 1800 284 789 to register in the first instance. You will be provided with a username and password that will enable you access to the test.

The expected time to complete this activity is 3 hours.

Do not send answers to the MCQs into the *check* office. This activity can only be completed online at http://gplearning.racgp.org.au

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

FOR A FULL LIST OF ABBREVIATIONS AND ACRONYMS USED IN THESE QUESTIONS PLEASE GO TO PAGE 3.

FOR EACH QUESTION BELOW SELECT ONE OPTION ONLY.

QUESTION 1

Rosemary, aged 36 years, is a marketing director. She has weekly manicures but in recent months she has only had shellac nail polish applied to her nails. She explains that shellac is a type of nail polish that is applied to natural nails. After each application (base coat, colour and top coat) the polish is cured briefly for seconds to several minutes under an ultraviolet lamp. The polish requires professional removal. Shellac allows Rosemary to have manicures less frequently as it lasts for several weeks.

Today she presents complaining that in recent months her nails have been chipping, splitting and flaking more so than usual. She believes these problems predate the use of shellac polish. Examination of her unvarnished nails reveals brittle nails with signs of splitting and flaking. The nail on her right thumb is splitting vertically at the midline, and the top third of the nail has separated from the nail bed. More than half of the nail is yellow/white in colour and there are no signs of thickening. Which of the following statements is NOT true?

A. An undiagnosed underlying disease could account for some of Rosemary's nail problems.

B. Her problems and, in particular, separation of her thumb nail from the nail bed may be due to aggressive manicure technique or repetitive trauma arising from frequent manicures.

C. Rosemary may have a fungal infection in her thumb nail.

D. Clinical examination is usually all that is required to identify a fungal nail infection.

E. In cases such as this, differential diagnosis could include bacterial infection, psoriasis and eczema/dermatitis.

QUESTION 2

Which of the followings statements regarding psoriasis and eczema is NOT true?

A. Topical steroids are generally first-line options for both conditions and antibiotics may be required to manage secondary infections in eczema.

B. Non-pharmacological management strategies should be discussed with people who have psoriasis or eczema.

C. A major difference between psoriasis and eczema is that psoriasis always requires life-long monitoring of patients.

D. Complementary therapies could be offered as adjunct therapies in both eczema and psoriasis.

E. Avoidance of irritants and factors known to exacerbate both psoriasis (e.g. hot water, soap, stress) and eczema (e.g. soap) should feature in any management plan for both conditions.

QUESTION 3

Joe, a farmer aged 61 years, presents requesting a tetanus injection after a mishap on the farm. He casually mentions a small lesion on his forearm. On examination, there is a small, pink/red, slightly inflamed papule on his distal forearm, measuring approximately 3 x 3 mm. Which of the following options is TRUE?

A. As Joe had a melanoma removed 10 years ago one could assume that this lesion may be a melanoma and may be an AHM even though the lesion is pigmented.

B. Use of dermoscopy may assist with differential and provisional diagnosis of this lesion and AHM cannot be ruled out at this stage.

C. In order to establish a definitive diagnosis a medical history should be taken and an excision biopsy should be performed.

D. A, B and C are correct.

E. B and C are correct.

QUESTION 4

Jason, aged 61 years, is a former professional footballer. He attends your practice complaining of funny looking toes, which he claims have slowly become weird over many months. On examination you notice that the nails on the big toes of both feet are yellowish in colour. The right toe is worse than the left: 80% of the nail is discoloured and there is nail thickening and some lifting of the nail from the nail bed. There is also some crumbling of both nails. You suspect a fungal nail infection. Which of the following options is the best one for management of Jason's nails?

A. You recommend a topical over-the-counter agent and tell him that he will need to use it for a long time.

B. You recommend oral terbinafine as this is the treatment of first choice according to current guidelines.

C. You suggest that the combination of a topical therapy with an oral antifungal is the best option as this has been shown to improve outcomes.

D. You recommend laser nail therapy as this technique is minimally invasive, has a quick turnaround time and produces high cure rates.

E. You advise Jason that you need to take nail samples to confirm your presumptive diagnosis microbiologically before any treatment can commence and ask him to make a follow-up appointment to see you to discuss his laboratory results and a management plan.

QUESTION 5

Jackson, aged 7 months, has been brought in by his mother to discuss her concerns about a very itchy, recent-onset rash on his face and body. On examination the rash appears red and dry, and is slightly cracked and weepy in areas. Examination reveals a rash on his face and behind his ears. His scalp is unaffected. Tiny patches of rash are also starting to appear on his limbs. Further questioning reveals that Jackson has been formula-fed and was started on solids in the last two months. There is a history of atopy on both sides of the family. Jackson's father was diagnosed with asthma at age 9 years. Which of the following statements is NOT correct?

A. Given Jackson's age, family history and presenting symptoms he may have atopic eczema.

B. In children, chronic severe asthma can lead to major sequelae, such as growth retardation.

C. Hydrocortisone (1%) would be an appropriate first-line topical treatment for Jackson's eczema.

D. Apart from a topical steroid no other therapy(s) will be required for Jackson.

E. If Jackson's eczema does not show improvement with treatment it would not be unreasonable to consider the possibility of allergy and/or secondary infection.

QUESTION 6

David, aged 26 years, is a personal trainer at a local gym. He presents complaining of foot pain. He has noticed bumpy growths on the sole of his foot, which have presented over a number of months. They have been increasing size, are starting to feel uncomfortable and are now causing him pain on walking. Given that he is on his feet all day for work he wants to know if these growths can be removed. Examination reveals typical cauliflower-like lesions on the sole of his feet. Which of the following statements is NOT correct?

A. Underlying comorbidities do not impact on management options for people with warts.

B. Most warts are generally diagnosed on the basis of clinical appearance rather than by biopsy or culture.

C. Differential diagnosis of raised lesions, such as warts, could include solar keratosis, squamous cell carcinoma, basal cell carcinoma and embedded foreign body.

D. Different human papillomavirus strains have been implicated in genital warts, compared with other types of warts.

E. Salicylic acid topical therapy and cryosurgery have been shown to produce similar results.

QUESTION 7

Simon, a lawyer aged 53 years, presents complaining of recent-onset joint pain and tiredness. He has had longstanding psoriasis, which was diagnosed several decades ago. He is confident in managing his psoriasis using a number of treatment modalities, including topical steroids and UV lamp therapy. He is into 'clean living', meditates to manage stress, eats well and exercises regularly. Which of the following is NOT true?

A. Ongoing attention to stress management is useful for people with psoriasis.

B. Simon's joint pain is not related to his psoriasis.

C. Even though Simon's psoriasis is well controlled he should be reviewed annually.

D. People with psoriasis should be asked questions about their psychological and social wellbeing and any problems identified should be managed.

E. Given the potential impact of psoriasis on long-term mortality and morbidity, it is important to monitor risk factors for cardiovascular disease, diabetes and depression.

QUESTION 8

While lasers have been used medically for many decades, in recent times the use of lasers has been expanded substantially to include a variety of common skin problems, including removal of cutaneous warts and treatment of fungal nail infections. Which of the following statements is NOT true regarding the use of lasers?

A. The quality of training provided to the individual performing laser therapy may influence treatment outcomes.

B. Laser therapy can be successfully used to treat wart virus and fungal nail infections.

C. Treatment of fungal toenail infections using laser therapy takes more time than traditional topical treatment options.

D. Laser therapies are typically minimally invasive, compared with other treatment options for both warts and fungal nail infections.

E. A, B and D are correct.

QUESTION 9

Jane, a student aged 16 years, presents with her mother to discuss an itchy, red, scaly rash on her hands, elbows and knees. She has had the rash for a number of months and it seems to be getting worse. She has been using a natural 'organic' body moisturiser, which was a birthday gift, on her skin. Jane had eczema as a child and her mother is concerned that her eczema is returning. Her mother is also concerned

that this might be psoriasis as her father had this problem when he was alive. Which of the following is true?

A. Careful examination of all of the skin on Jane's body should be undertaken before a diagnosis is made.

B. While topical steroids are the treatment of choice for both eczema and psoriasis, consideration should also be given to the incorporation of non-pharmacological strategies in the treatment plan.

C. Should this rash prove to be eczema Jane will require life-long follow up.

D. A, B and C are correct.

E. A and B are correct.

QUESTION 10

Amelanotic/hypomelanotic malignant melanoma (AHM) is a subtype of melanoma where lesions present with little or no pigment on visual inspection. It may mimic benign and malignant variants of both melanocytic and non-melanocytic lesions, which may lead to delayed clinical diagnosis. Which of the following statements is NOT true?

A. Use of dermoscopy significantly increases the chances of diagnostic accuracy in AHM.

B. Consideration should be given to following up initial AHM biopsy results with referral to a specialist centre for wider excision and possible sentinel node biopsy.

C. Clinicians should be hyper-vigilant when examining amelanotic and/or hyomelanotic lesions

D. The various established dermoscopic rules and criteria are very helpful with the diagnosis of AHM.

E. AHM requires long-term management of patients, who may also require emotional counselling and support.

check

Independent learning program for GPs

Unit 503 March 2014

Heart health

RACGP

www.racgp.org.au/check

Subscriptions

For subscriptions and enquiries please call 1800 331 626 or email check@racgp.org.au.

Published by

The Royal Australian College of General Practitioners
100 Wellington Parade
East Melbourne, Victoria 3002, Australia
Telephone 03 8699 0414
Facsimile 03 8699 0400
www.racgp.org.au

ABN 34 000 223 807
ISSN 0812-9630

check

Independent learning program for GPs

Heart health

Unit 503 March 2014

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

Despite the improvements in cardiovascular health, cardiovascular disease (CVD) remains a leading cause of disability, illness and premature death, and is the most expensive disease group in Australia.[1,2] The prevalence of CVD in Australians is predicted to increase in the next decades.[1]

CVD is associated with a number of risk factors, many of which are preventable or modifiable[1] (e.g. lifestyle factors such as smoking, obesity), indicating a role for preventive strategies.[3] General practitioners (GPs) play a critical part in CVD preventive activities[3] and are central to the long-term management of people with CVD by identifying risk factors and navigating patients through the healthcare system for acute care and secondary prevention. However, in 2010 the National Heart Foundation (NHF) reported[2] a significant gap between guideline recommendations for the management of CVD and actual clinical practice.

The NHF has called for the implementation of preventive measures and improved management of people with CVD or at risk of CVD. Of relevance for GPs, one of the NHF's key prevention initiatives is a cardiovascular health check in general practice and use of the CVD risk assessment to identify people at high risk of CVD and commence treatment where necessary.[2]

This unit of *check* will explore the management of common presentations of CVD in general practice.

LEARNING OUTCOMES

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

- describe pharmacological and non-pharmacological options for managing the signs and symptoms of heart failure
- compare and contrast the risks and benefits of warfarin versus the newer oral anticoagulant agents
- describe anticoagulant protocols for management of superficial venous thromboembolism, deep vein thrombosis and pulmonary embolism
- describe the benefits of using a cardiovascular risk assessment calculator when making clinical decisions for patients
- outline appropriate management strategies and resources available to family members following sudden cardiac death of a loved one.

AUTHORS

Sam Hayman BSc, MSc, MBBS (Hons) is an Advanced Trainee in Cardiology at the Royal Brisbane and Women's Hospital. He has special interests in heart failure and coronary artery disease.

John Atherton MBBS, PhD, FRACP, FCSANZ is Director of Cardiology at the Royal Brisbane and Women's Hospital and Associate Professor, Department of Medicine, University of Queensland. He has special interests in heart failure, cardiac genetics and cardiac rehabilitation.

Julie McGaughran BSc (Hons), MBChB (Hons), MD, FRCP, FRACP is the Director of Genetic Health Queensland and an Associate Professor at the University of Queensland. She has special interests in dysmorphology, cardiac genetics and legal and ethical issues in clinical genetics.

Louise McCormack BsC, BCom, MBBS is an advance trainee in Cardiology at the Royal Brisbane and Women's Hospital.

Kate Johnston MBBS FRACGP is a general practitioner and GP Liaison Officer for Gold Coast University Hospital and Gold Coast Medicare Local. Her interests are quality use of medicines and optimising integrated care and communication at the hospital-primary care interface.

Deanna Devers BMus, MMus, PhD, BMBS is a general practice registrar working in Hobart. She has a background in teaching and research.

Mark Kennedy MBBS, BMedSc (Hons), Grad Dip Fam Med is a general practitioner in Geelong, Victoria and clinical director of Northern Bay Health, a network of three medical clinics and a community-based diabetes centre. He has special interests in diabetes, chronic disease management and health and medical law. He is involved in the education of medical students, GP registrars and GPs at state, national and international levels, and in primary care research.

PEER REVIEWERS

Mark Beeby MBBS, FRACGP Dip Pal Med, has worked in a group general practice in Lalor for 31 years. He has been an FRACGP examiner for 21 years, a clinical supervisor associated with VMA, and was a member of the Cardiovascular Expert Group for Therapeutic Guidelines Cardiovascular (version 6) in 2012. He is also a board member of Infiniti Health Solutions.

Mark Nelson MBBS (Hons), MFM, PhD, FRACGP, FAFPHM is a Professorial Research Fellow at Menzies Research Institute Tasmania, University of Tasmania.

REFERENCES

1. Australian Institute of Health and Welfare 2011. Cardiovascular disease. Available at www.aihw.gov.au/WorkArea/DownloadAsset.aspx?id=10737418530) [Accessed 14 February 2014].
2. National Heart Foundation of Australia. Improving cardiovascular health outcomes in Australian general practice. Available at www.heartfoundation.org.au/SiteCollectionDocuments/General-Practice-Policy-Paper.pdf [Accessed 14 February 2014].
3. The Royal Australasian College of General Practice. Guidelines for preventive activities in general practice. 8th Edn. East Melbourne 2012. Available at www.racgp.org.au/download/Documents/Guidelines/Redbook8/redbook8.pdf [Accessed 18 February 2014].

GUIDE TO ABBREVIATIONS AND ACRONYMS IN THIS UNIT OF *CHECK*

ACEI	angiotensin-converting enzyme inhibitor	GFR	glomerular filtration rate	NSTEMI	non-ST segment elevation myocardial infarction
AF	atrial fibrillation	HDL	high density lipoprotein	NYHA	New York Heart Association
BNP	B-type natriuretic peptide	HR	heart rate	PBS	Pharmaceutical Benefits Scheme
BP	blood pressure	INR	international normalised range	PE	pulmonary embolism
BPM	beats per minute	JVP	jugular venous pressure	SCD	sudden cardiac death
CAD	coronary artery disease	LBBB	left bundle branch block	TC	total cholesterol
CMI	consumer medicine information	LDL	low density lipoprotein	TG	triglycerides
CrCl	creatinine clearance	LMWH	low molecular weight heparin	TIA	transient ischaemic attack
CT	computerised tomography	LV	left ventricular	TRAGEDY	Trans-Tasman response Against Sudden death in the Young
CVD	cardiovascular disease	LVEF	left ventricular ejection fraction	TSH	thyroid stimulating hormone
DVT	deep vein thrombosis	LVH	left ventricular hypertrophy	TTR	time in therapeutic range
ECG	electrocardiogram	MRA	mineralocorticoid receptor antagonist	uARC	urine albumin-to-creatinine
EEG	electroencephalogram	MRI	magnetic resonance imaging		
FBG	fasting blood glucose				

CASE 1

RUSSELL IS SHORT OF BREATH

Russell is a truck driver aged 68 years and is new to your practice. He describes progressive dyspnoea that he has had for the past three months and is now breathless when showering and dressing. For the past week he has felt more comfortable overnight sleeping on three pillows.

Russell says he had a heart attack 15 years ago, which was treated with a stent, and has had no chest pain since then. He has had problems with high blood pressure and cholesterol. His medications are aspirin 100 mg mane, perindopril 5 mg mane, atenolol 50 mg mane and atorvastatin 40 mg daily.

Russell is married and has two children. He stopped smoking when he had his heart attack and drinks a small amount of alcohol.

On examination his heart rate (HR) is 90 bpm and regular, and blood pressure (BP) is 150/90 mmHg. Jugular venous pressure (JVP) is difficult to measure but you think it is slightly elevated. There is a soft systolic murmur at the apex. The chest is clear. He has mild bipedal pitting oedema.

QUESTION 1

What is your provisional diagnosis? What initial investigations will you order? What initial therapy will you start?

FURTHER INFORMATION

Russell's electrocardiogram (ECG) is shown below. Biochemistry results are: Na 135 mmol/L; K 4.2 mmol/L; urea 8.9 mmol/L; creatinine 98 µmol/L; eGFR (MDRD) 69 mL/min. Full blood count is normal; BNP is 1680 ng/L (normal <50 ng/L). A chest X-ray shows an increased cardiothoracic ratio and clear lung fields. The ECG shows a dilated left ventricle with severe systolic dysfunction (left ventricular ejection fraction (LVEF) 25% with anterior akinesia) and moderate mitral regurgitation. Russell's dyspnoea improves with frusemide.

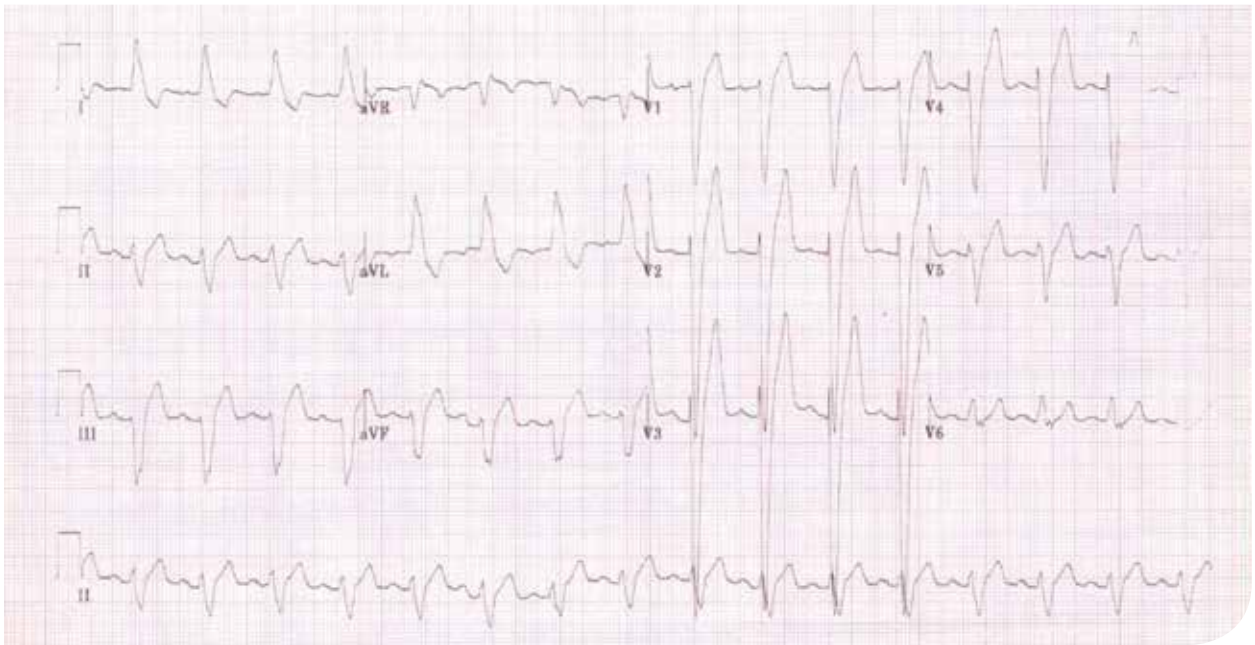

Figure 1. Russell's ECG results

QUESTION 2

What does Russell's ECG show? What is his diagnosis?

QUESTION 3

Which patients should be referred for specialist opinion?

QUESTION 4

What non-pharmacological recommendations, if any, do you make for Russell?

QUESTION 5

Which drugs have been shown to decrease mortality in systolic heart failure? How will you achieve maximum tolerated doses of these medications?

QUESTION 6

How should patients taking mineralocorticoid receptor antagonists (MRA), such as spironolactone, be monitored?

QUESTION 7

What will you tell Russell about driving?

FURTHER INFORMATION

Russell is seen by a cardiologist. A coronary angiogram reveals a patent stent with diffuse distal disease not amenable to revascularisation. His LVEF is 30%. Russell now takes aspirin 100 mg mane, perindopril 10 mg mane, carvedilol 50 mg twice daily, spironolactone 50 mg mane and atorvastatin 40 mg daily. He is in sinus rhythm with a heart rate of 80 bpm, and blood pressure 100/50 mmHg.

QUESTION 8

How important is heart rate reduction in treating heart failure? When should a sinus node inhibitor (i.e. ivabradine) be added?

QUESTION 9

Which patients should be considered for device therapy?

FURTHER INFORMATION

Following discussion with the cardiologist, Russell decides to defer device therapy as there has been some improvement in his LVEF. A repeat echocardiogram 3 months later demonstrates a LVEF of 40%, and Russell remains symptomatically well.

CASE 1 ANSWERS

ANSWER 1

You suspect that Russell's dyspnoea may be due to heart failure, given his history of previous myocardial infarction and hypertension. He currently displays New York Heart Association (NYHA) functional class III symptoms[3] (see *Table 1*).

Table 1. New York Heart Association functional classification of heart failure[3]

Class	Symptoms
Class I (mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, dyspnoea or palpitations (asymptomatic LV dysfunction).
Class II (mild)	Slight limitation of physical activity. Ordinary physical activity results in fatigue, dyspnoea, angina or palpitations.
Class III (moderate)	Marked limitation of activity. Less than ordinary physical activity leads to symptoms.
Class IV (severe)	Severely limited by symptoms. Symptoms present at rest.

Initial investigations should include ECG, blood tests (biochemistry, full blood count) and chest X-ray.[3,4] Given that he has had longstanding elevated blood pressure, urine albumin-to-creatinine ratio (uACR) should also be measured, but blood pressure control is not the goal of treatment. However, none of these tests allows you to exclude a diagnosis of heart failure, so further investigation is required.

The most useful test to perform in patients with suspected heart failure is an echocardiogram, which provides information on cardiac structure, systolic and diastolic function and valvular function.[3]

Routine measurement of plasma B-type natriuretic peptide (BNP) is not recommended for diagnosis of chronic heart failure; however, if an echocardiogram cannot be arranged in a timely fashion, plasma BNP measurement may be useful.[3] A low BNP level (<100 ng/L) makes the diagnosis of heart failure unlikely, and alternative diagnoses should be considered.[5]

Angiotensin converting enzyme inhibitors (ACEIs) are first-line treatment for heart failure of any class. They should be commenced immediately, at a low dose, with the view to titrating the dose over intervals (e.g. 2–4 weeks) to maximally tolerated maintenance doses as per current guidelines.[2,6]

As Russell is already taking an ACEI, you start frusemide 40 mg mane for control of fluid overload symptoms.[2,4]

ANSWER 2

The ECG shows sinus rhythm of 97 bpm with left bundle branch block (LBBB): QRS >120 ms, positive broad complex in I, aVL, V5 and V6. The ST segment deviation is as expected for LBBB.

The cause of Russell's dyspnoea is heart failure (elevated BNP, symptomatic response to frusemide, LVEF 25%) due to severe left ventricular (LV) systolic dysfunction (systolic heart failure), underlying coronary artery disease (CAD) and previous myocardial infarction.

ANSWER 3

Ideally, a specialist opinion should be sought for all heart failure patients as referral improves patient symptoms, outcomes and reduces hospital admissions.[3] As a minimum this should include: i) when the diagnosis is in question; ii) when there are questions regarding management; iii) when a patient is being considered for revascularisation, a cardiac device or cardiac transplant; and iv) in patients under 65 years of age.[3]

ANSWER 4

Current heart failure guidelines recommend a range of non-pharmacological management strategies for patients.[3,4]

People with heart failure should be provided with information to enable them to monitor and manage their fluid balance. As high salt intake can exacerbate heart failure symptoms, restriction of both sodium (<2 g/day) and fluid (<2 L/day) is recommended. A lower fluid intake (<1.5 L/day) is advised for patients during episodes of fluid retention.[3] Patients can monitor their fluid status by measuring their morning weight before breakfast.

Once heart failure is stabilised, regular physical activity is advised to improve symptoms and functional capacity. Referral to a physical activity specialist could also be considered to enable individual tailoring of an exercise program.[3,7]

All patients should be advised about healthy lifestyle strategies. For example, quitting smoking if smokers, limiting alcohol to less than 1–2 standard drinks per day and limiting caffeinated beverages to 1–2 drinks per day.[2]

Dietary assessment and advice could also be considered as people with heart failure may become nutritionally deficient.[4]

Prevention strategies that could be discussed include vaccination against influenza and pneumococcal disease.[3]

ANSWER 5

ACEIs (or angiotensin receptor blockers in patients intolerant of ACEIs), heart failure beta-blockers (carvedilol, bisoprolol, metroprolol succinate, nebivolol) and MRA (i.e. spironolactone or eplerenone) prolong survival in patients with symptomatic systolic heart failure.[3,8–14] Digoxin has not been shown to reduce mortality; however, it reduces hospitalisations for heart failure, maintains clinical stability and exercise capacity in patients.[6]

Optimisation or the achievement of maximally tolerated doses of medications may take months (especially for beta-blockers), and requires close monitoring of symptoms, fluid status, kidney function and electrolytes.[4] 'Start low and go slow' is the generally accepted mantra. Beta-blockers should be initiated when the patient is stable and euvolaemic.[4] A Heart Failure Service with a titration prescription can facilitate this (www.health.qld.gov.au/heart_failure/pdf/medn_titration.pdf).

You continue frusemide 40 mg mane, increase perindopril to 10 mg mane, change atenolol to carvedilol, starting with a dose of 6.25 mg orally twice daily and aiming to increase the dose to 25–50 mg twice daily[4] and add spironolactone 25 mg mane (and consider uptitration to 50 mg mane). You refer Russell to a cardiologist.

ANSWER 6

Mineralocorticoid receptor antagonists (MRAs) improve survival and reduce hospital admissions in people with heart failure.[4] They can be initiated if the patient's potassium level is normal and there is adequate renal function. The RALES trial[14], which evaluated the benefits of spironolactone in heart failure, excluded patients with creatinine levels >221 µmol/L. In patients with renal failure, the addition of an MRA to an ACEI or an angiotensin-2 receptor antagonist can lead to life-threatening hyperkalaemia.[4]

Note, several contraindications apply for the use of MRAs. Spironolactone and eplerenone are contraindicated if the creatinine clearance (CrCl) is <30 mL/min of if the serum potassium is >5.5 mmol/L.[6]

Monitoring of potassium and renal function closely is mandatory for people on MRAs,[6] e.g. 1 week after commencing or titrating the dose, monthly for 6 months and then 6 monthly thereafter once stable dosing is achieved (see www.health.qld.gov.au/heart_failure/pdf/medn_titration.pdf).

ANSWER 7

The medical standards for driving a private vehicle stipulate that there must be a response to treatment and minimal symptoms associated with driving. Where these conditions are met, a conditional licence subject to periodic review (a specific time frame is not indicated) will be issued.

A commercial driver's licence requires that the patient has a satisfactory response to treatment, adequate exercise tolerance, LVEF ≥40%, have had the underlying cause considered and have minimal symptoms related to driving. Where these conditions are met a conditional licence subject to annual review will be issued (see Resources for Doctors for the Assessing Fitness to Drive guidelines).

ANSWER 8

Elevated resting heart rate is a predictor of death and hospitalisation in heart failure.[15,16]

Ivabradine is a specific sinus node inhibitor, which inhibits the sinoatrial 'pacemaker' current, leading to a reduction in heart rate.[17] It improves outcomes in patients with symptomatic systolic heart failure (LVEF ≤35%) in sinus rhythm with an elevated heart rate (≥70 bpm) despite optimal therapy.[3,8] According to the SHIFT study,[18] the main heart failure trial for ivabradine, its benefits are greater in patients with higher heart rates, with a 19% reduction in mortality seen in patients with heart rates ≥77 bpm. Additionally, significant reductions in hospitalisations were also observed.[18] A number needed to treat of 26 was calculated in the SHIFT trial. That is, 26 patients needed to be treated for one year to prevent one cardiovascular death or one hospitalisation from chronic heart failure.[18]

Ivabradine is available on the Pharmaceutical Benefits Scheme (PBS) with multiple restrictions and requires an authority script. As of December 2013, patients with chronic heart failure with a baseline heart rate ≥77 bpm, LVEF ≤35% and NYHA class II or III, in combination with optimal standard chronic heart failure treatment were eligible for PBS therapy.[17] Therapeutic Guidelines Cardiovascular[4] recommends doses of 2.5 to 7.5 mg (orally) twice daily. Note, that ivabradine may be prescribed by nurse practitioners where treatment has been previously initiated by a medical practitioner.[17]

Ivabradine is contraindicated if the heart rate is <60 bpm in the untreated state, where the sinoatrial node is not the cardiac pacemaker, in unstable angina, in unstable or acute heart failure or if the BP is <90/50 mmHg. Its use is also contraindicated in severe hepatic impairment.[6]

Russell meets the PBS criteria, and it would be appropriate to start ivabradine 5 mg twice daily in addition to his other therapy with a view to titrate up if the heart rate remains elevated.

ANSWER 9

In addition to the reductions in mortality associated with medical therapy, implantable cardioverter defibrillators have been shown to further decrease mortality in symptomatic heart failure patients with a LVEF ≤35%,[19] and in patients with prior myocardial infarction and a LVEF ≤30%.[20]

Cardiac resynchronisation therapy (biventricular pacing) decreases mortality in patients with symptomatic heart failure with a LVEF ≤35% and a broad QRS. Benefit is greatest in LBBB with a QRS ≥150 ms.[21–23]

CONCLUSION

Current evidenced-based guidelines emphasise the benefits of multidisciplinary, guideline-based care for people with heart failure. People receiving multidisciplinary care achieve better outcomes than patients who do not.[1] A number of tools are available to assist GPs managing patients requiring multidisciplinary care, including the GP Management Plan (Item 721) and for review (Item 725) as well as Team Care Arrangements coordinated by the GP (Item 723) and for review (Item 727). As an example, a multidisciplinary team might consist of the GP, an exercise physiologist and a dietician.[2]

Current guidelines highlight important gaps in the management of people with heart failure and suggest that greater attention in certain areas may improve patient outcomes. For example, this includes greater use of echocardiography, which is currently underused at diagnosis and for ongoing assessment of patients. Studies show that both ACEIs and beta-blockers are generally under-prescribed and used at suboptimal doses. Lastly, clinicians need to mindful of not prescribing medications that may exacerbate heart failure, as prescribing of such medications (e.g., corticosteroids, moxonidine) is common.[2]

REFERENCES

1. National Heart Foundation of Australia. A systematic approach to chronic heart failure: a consensus statement August 2013. Available at www.heartfoundation.org.au/SiteCollectionDocuments/HF_CHF_consensus_web_FINAL_SP.pdf [Accessed 3 February 2014].
2. National Heart Foundation of Australia. Quick reference guide for health professionals. Diagnosis and management of chronic heart failure. Updated October 2011. Available at www.heartfoundation.org.au/SiteCollectionDocuments/Chronic-heart-failure-QRG-2011.pdf [Accessed 3 February 2014].
3. National Heart Foundation of Australia. Guidelines for the prevention, detection and management of chronic heart failure in Australia 2011. Available at www.heartfoundation.org.au/SiteCollectionDocuments/Chronic_Heart_Failure_Guidelines_2011.pdf [Accessed 3 February 2014].
4. Cardiovascular Expert Group. Heart Failure. In: eTG [Internet]. Melbourne: Therapeutic Guidelines Ltd; 2012. Available at www.tg.org.au [Accessed 3 February 2014].
5. Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002;347:161–67.
6. Rossi S, editor. Heart failure. Australian Medicines Handbook. In: Australian Medicines Handbook 2013. Adelaide: Australian Medicines Handbook Pty Ltd; 2013.
7. O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure (HF-ACTION). JAMA 2009;301:1439–50.
8. Krum H, Jelinek MV, Stewart S, et al. 2011 Update to national heart foundation of Australia and cardiac society of Australia and New Zealand guidelines for the prevention, detection and management of chronic heart failure in Australia 2006. MJA 2011;194:405–09.
9. Shibata MC, Flather MD, Wang D, et al. Systematic review of the impact of beta blockers on mortality and hospital admissions in heart failure. Eur J Heart Failure 2001;351–57.
10. McMurray JJV, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. Eur Heart J 2012;33:1787–47.
11. Flather MD, Yusuf S, Kober L, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left ventricular dysfunction: A systematic overview of data from individual patients. Lancet 2000;355:1575.
12. Pfeffer MA, Swedberg K, Granger CB, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet 2003;362:759–66.
13. Zannad F, McMurray JJ, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms (EMPHASIS). N Engl J Med 2011;364:11–21.
14. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure (RALES). N Engl J Med 1999;341:709.
15. Bohm M, Swedberg K, Komajda M, et al. Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial. Lancet 2010;376:886–94.
16. Pocock SJ, Wang D, Pfeffer MA, et al. Predictors of mortality and morbidity in patients with chronic heart failure. Eur Heart J 2006; 27:65–75.
17. NPS MedicineWise. Ivabadrine (Coralan) for chronic heart failure. Available at www.nps.org.au/publications/health-professional/nps-radar/2013/december-2013/ivabradine [Accessed 3 February 2014].
18. Swedberg K, Komajda M, Bohm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomized placebo-controlled study. The Lancet 2010;376:875–85.
19. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure (SCD-HeFT). N Engl J Med 2005;352:225–37.
20. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction (MADITII). N Engl J Med 2002;346:877–83
21. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure (COMPANION). N Engl J Med 2004;350:2140–50.
22. Cleland JGF, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure (CARE-HF). N Engl J Med 2005;352:1539–49.
23. Tang ASL, Wells GA, Talajic M, et al. Cardiac-resynchronization therapy with mild-moderate heart failure (RAFT). N Engl J Med 2010;363:2285–95.

RESOURCES FOR DOCTORS

- 2011 Guidelines for the prevention, detection and management of chronic heart failure in Australia. Heart Foundation www.heartfoundation.org.au/SiteCollectionDocuments/Chronic_Heart_Failure_Guidelines_2011.pdf
- Assessing Fitness to Drive. www.austroads.com.au/images/stories/AFTD_reduced_for_web.pdf

RESOURCES FOR PATIENTS

- Heart Foundation Information Booklet – Cardiomyopathy. www.heartfoundation.org.au/SiteCollectionDocuments/Cardiomyopathy.pdf

CASE 2

CHRISTINE PRESENTS WITH FATIGUE

Christine, aged 76 years, presents requesting a repeat prescription of her blood pressure (BP) medication. She was recently widowed and moved to the area to be closer to her daughter. She has no specific concerns but admits she has been a little more tired than usual, which she attributes to her bereavement. She reports general good health. Her BP is 135/80 mmHg with irbesartan 150 mg mane. Examination reveals an irregular heart rate (HR) of 116 bpm and atrial fibrillation (AF) is confirmed on a 12-lead ECG. She had attended her local GP in her previous town regularly for many years but was never aware of this diagnosis.

QUESTION 1

What additional history and investigation is required?

FURTHER INFORMATION

Christine's thyroid stimulating hormone (TSH) level is normal as is her echocardiogram. A diagnosis of non-valvular AF is confirmed. She has monitored her pulse over the past week and it has remained irregular, as is found when reviewed in clinic.

QUESTION 2

How should AF be managed?

QUESTION 3

What anticoagulation options are available to Christine and what considerations should be given to each?

FURTHER INFORMATION

Christine elects to commence warfarin treatment, as her husband tolerated it well for years. She manages well and settles into a monthly pattern of INR monitoring, which is generally stable. After 2 years she leaves the area to live with her son in Central Queensland.

She returns to see you 12 months later, staying with her daughter again, and is scheduled to have neurosurgery in 2 weeks for back pain. While in Central Queensland she was switched to dabigatran owing to the inconvenience of travelling long distances for INR monitoring.

QUESTION 4

How should anticoagulation therapy be managed peri-operatively?

CASE 2 ANSWERS

ANSWER 1

AF may occur in the context of underlying disease (e.g. hypertension, mitral valve disease, hyperthyroidism, ischaemic heart disease, heart failure, sleep apnoea)[1] or in the absence of other diseases. Evidence of underlying disease should be sought through history and investigation. In addition, precipitating factors for an episode of AF should be sought:[1] excess alcohol and/or caffeine consumption, and smoking status (including marijuana).[2]

A number of standard investigations may be considered for the initial evaluation of people presenting with AF, with the aim of evaluating cardiac function at baseline and identifying common comorbid conditions. These include:

- a complete blood count to identify underlying conditions (e.g. anaemia, infection)
- a complete metabolic profile for identification of electrolyte problems that may be causing or exacerbating AF
- echocardiography to assess heart features (e.g. size, shape, chamber pressures, valve structure and function, and systolic/diastolic function)
- electrocardiography to diagnose AF or to identify other arrhythmias and/or cardiac conditions (e.g. ischaemia)
- chest radiography to identify underlying pulmonary disease (e.g. pneumonia)
- additional tests as required on the basis of findings from the above tests.[3]

Appropriate investigations to consider for Christine could include full blood count (FBC), electrolytes and liver function tests (LFTs), measurement of TSH levels to assess thyroid function, and echocardiogram to assess valvular function. It is reasonable to request these tests, given that treatment will probably be necessary.

ANSWER 2

AF has been associated with an increased mortality risk. It has been described as conferring a 5-fold increase in the risk of stroke and a 3-fold increase in the risk of heart failure.[4]

As Christine is well and haemodynamically stable the principles of management for AF are based on:

- rate control and rhythm control to reduce symptoms and morbidity
- consideration of prophylaxis against thromboembolic complications.[1,5]

As this is her first presentation, the clinical pattern (paroxysmal, persistent or permament)[1,5] is not yet established. However, she has tachycardia, has felt tired and has continued to have clinically detectable tachyarrhythmia.

Rate control medication is suitable for minimally symptomatic patients. Rate control was demonstrated in the AFFIRM study, a large randomised trial with 4060 patients, to be at least as effective as rhythm control and had fewer side effects.[5,6] Beta blockers (metoprolol or atenolol) or calcium channel blockers (diltiazem or verapamil) are suitable.[1] Of particular importance is consideration of anticoagulant treatment. An Australian hospital audit in 2011 found that 70% of patients admitted with stroke in AF were not on anticoagulant treatment.[7]

All patients with AF should undergo a systematic assessment of their risk of thromboembolism and bleeding to assist with informed decision-making about anticoagulation therapy. NPS MedicineWise offers a practical solution to this assessment,[8] which outlines three steps:

1. Patient assessment
2. Risk mitigation
3. Anticoagulant selection.

Step 1: Non-valvular AF patient assessment – CHADS $_2$ score calculator[9]

Current guidelines[1,5] recommend treatment of people with non-valvular AF on the basis of their calculated $CHADS_2$ score (*Tables 1 and 2*).

Table 1. $CHADS_2$ tool for estimation of thromboembolic risk in people with non-valvular AF

Risk factor	Score
Congestive heart failure	1
Hypertension (including well controlled hypertension)	1
Age 75 years or older	1
Diabetes mellitus	1
Stroke or history of transient ischaemic attack (TIA)	2

Table 2. Risk of stroke based on $CHADS_2$ score

Stroke risk based on CHADS $_2$ score	Risk of stroke	Adjusted stroke rate
0	Low	1.9%
1	Moderate	2.8%
2	High	4%
3	High	5.9%
4	High	8.5%
5	High	12.5%
6	High	18.2%

Christine is over 75 years of age and has hypertension. Her $CHADS_2$ score is 2 and her risk of stroke is high (4% per 100 patient years without treatment).

Oral anticoagulation treatment is recommended for those determined

to have a moderate-to-high risk of stroke (i.e. $CHADS_2$ score ≥1).[1,5] Current guidelines recommend either asprin or no therapy for a $CHADS_2$ score of 0, whereas for a $CHADS_2$ score of 1 either aspirin or an oral anticoagulant is recommended with a stated preference for the latter.[1,5] The evidence for aspirin (an antiplatelet agent) in stroke prevention in AF is weak, as it is less effective than oral anticoagulants. The risk of major bleeding with aspirin is similar to that of well-controlled warfarin.[1]

Step 2: Risk mitigation

The risk of major bleeding while on an oral anticoagulant treatment has been reported to be in the order of at least 1–1.5% annually; higher rates are reported for those over 80 years of age in the first year (up to 80%) and declines in ensuing years (down to 40%).[1]

The HAS-BLED tool (*Table 3*)[10] can be used to identify correctable risk factors for bleeding and identify patients at high risk of bleeding. It should not be used to exclude patients from anticoagulant treatment. Patients at high risk of bleeding are also at high risk of stroke and increased monitoring may be required.[4] Correctable risk factors for bleeding should be identified and where possible managed.[11]

Table 3. The HAS-BLED tool[10]

H	Hypertension (systolic blood pressure >160 mm Hg)*
A	Abnormal renal or liver function
S	Stroke (history of)
B	Bleeding (history of, or predisposition to bleeding)
L	Labile INRs (<6 in 10 INRs in therapeutic range)*
E	Elderly (e.g. age >65 years)
D	Drugs (antiplatelet agents, NSAIDs, or alcohol ≥ 8 units per week)*

*Correctable risk factors for bleeding

Referring to the HAS-BLED tool,[8] Christine has hypertension, which is controlled, and is over 65 years of age but has no other risk factors that increase her bleeding risk. She is happy to consider anticoagulant treatment to reduce her risk of stroke.

ANSWER 3

Four oral anticoagulant agents are currently available. These include warfarin or the newer oral anticoagulants dabigatran, rivaroxaban and apixaban, which were PBS-listed in 2013 for stroke prevention in non-valvular AF.[12–14] See *Table 4* for a comparison of these agents. It is important to discuss with Christine the risks and benefits of all of these drug options. NPS RADAR has articles available on the role and place of each of these new anticoagulants in therapy.[12–14]

It is worth noting that only a few large trials have assessed the efficacy and safety of the newer oral anticoagulant agents relative to warfarin and there is a paucity of head-to-head data comparing newer agents.[23] In contrast to warfarin, the new oral anticoagulant agents do not require monitoring (*Table 4*). The new agents have not been shown to reduce stroke or systemic embolism to a greater extent than warfarin for patients whose INR is maintained within the therapeutic range (i.e. time in therapeutic range (TTR) ≥66%).[23] Lastly, current Australian guidelines cite both warfarin and dabigatran as first-line options when oral anticoagulation is required in AF.[1]

In comparative trials where warfarin use was well managed, only apixaban (of the new agents) was shown to have a lower incidence of major bleeds, compared with warfarin.[23,24,27,28]

The newer oral anticoagulant agents (dabigatran, rivaroxaban and apixaban)[17,24–26] could be considered as alternatives to warfarin in the absence of significant valvular disease, where there is poor INR control in the presence of good adherence to warfarin and where the CrCl is >30 mL/min.[25] Additionally, the newer agents might be suitable for patients for whom regular blood testing is problematic or who are unable to tolerate warfarin.[12–14]

ANSWER 4

Patient features, such as age and history of bleeding, as well as the nature of the planned surgery, will influence decision making for ceasing and restarting new oral anticoagulant agents.[29] Consideration of bridging anticoagulant pre- and/or post-operatively might be appropriate for some patients (e.g. intravenous heparin or low molecular weight heparin for high-risk patients).[16,29] Decisions about the duration of peri-operative discontinuation of dabigatran depend on renal function as it is cleared predominantly by the kidneys.[30] It has a longer half-life (>24 hours) in people with reduced renal function (CrCl <30ml/min), compared with healthy volunteers (around 13 hours) who are considered to be representative of the target group likely to be using this medication.[31] For those with normal renal function medication can be ceased 24 hours before elective surgery.[30] Some guidelines provide tabulated data suggesting when the last intake of a new oral anticoagulation agent (including dabigatran) should occur, taking into consideration the risk of bleeding (high or low) and renal function.[22,29]

While the above more complex considerations might be relevant for some patients, it has been suggested that, ideally, dabigatran should be ceased at least 24 hours before invasive surgery and at least 48 hours before procedures associated with a high risk of bleeding.[30] As general guidance, the Therapeutic Guidelines 2012 suggest continuation of all regular antithrombotic medications in patients having a procedure or surgery with a low risk of bleeding.[1] The guidelines stipulate that for procedures or surgery with a high risk of bleeding, anticoagulants usually need to be discontinued for a period of time to reduce the risk of bleeding. The Australian Medicines Handbook recommends cessation of dabigatran treatment 1–3 days before surgery if CrCL is >50mL/min.[16] For patients with impaired renal function (CrCl 30–50 mL/min) it should be ceased 3–5 days before surgery. Consideration could be given to increasing these times where complete haemostasis is needed.[16]

Where there is immediate and complete haemostasis, dabigatran can be restarted post-operatively within 6–8 hours.[29]

Table 4. Comparison of warfarin with newer oral anticoagulants for non-valvular AF

	Warfarin[15]	Dabigatran[16]	Rivaroxaban[17]	Apixaban[19]
Mode of action	Vitamin K antagonist	Direct thrombin inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Dose	Follow local dosing protocols and adjust dose according to INR (target 2–3)	150 mg orally twice daily Dose reduction to 110 mg twice daily for patients aged ≥75 years or for those with a (potentially) higher risk of bleeding;[1] and those with CrCl <30–50 mL/min[1,16]	20 mg once daily[#]	5 mg twice daily
PBS status	No restrictions	Authority required (streamlined)[19]	Authority required (streamlined)[20]	Authority required (streamlined)[21]
Antidote (for overcoagulation)	Available (vitamin K)	Not available	Not available	Not available
Renal considerations	Dose adjustments based on renal function per se are not required (use with care in severe renal impairment due to increased risk of bleeding)	Contraindicated if CrCl <30 mL/min Reduce dose in renal impairment (CrCl 30–50 mL/min)	Contraindicated if CrCl <29 mL/min Use with caution if CrCl 30–49 mL/min and using drugs that may increase rivaroxaban concentration	Contraindicated if CrCl <15 mL/min Use with caution when CrCl 15–29 mL/min (apixaban concentrations may increase)
Monitoring	Routine INR monitoring is required to maintain INR within target levels	Routine testing is generally not conducted[22] Measuring activated partial thromboplastin time determines if a dabigatran effect is present but does not provide data on the extent of anticoagulant activity[1] INR monitoring not recommended[22]	Routine laboratory monitoring is not recommended as there are no methods to guide dose adjustment	Routine laboratory monitoring not recommended as there are no methods to guide dose adjustment
Adverse events	Common: bleeding Rare: skin necrosis, purple discolouration of toes, alopecia, fever, rash, nausea, vomiting, diarrhoea, hepatic dysfunction, allergic reactions	Common: bleeding from puncture sites and wounds, signs of bleeding (e.g. anaemia) gastritis, dyspepsia, gastrointestinal bleeding Infrequent: increased liver enzymes and bilirubin Rare: severe bleeding	Common: bleeding, signs of bleeding (e.g. anaemia), peripheral oedema, itch, skin blisters, muscle spasm	Common: bleeding, signs of bleeding (e.g. anaemia), nausea Infrequent: thrombocytopaenia, abnormal liver function tests Rare: allergic reactions

[#]Reduce dose to 15 mg once daily if CrCl is 30–49 mL/min[17]

REFERENCES

1. Cardiovascular Expert Group. Therapeutic guidelines: cardiovascular. Version 6. In: eTG [Internet]. Melbourne: Therapeutic Guidelines Ltd; 2012. Available at www.tg.org.au [Accessed 3 February 2014].
2. Crawford MH. Current Diagnosis and Treatment Cardiology 3rd ed. McGraw-Hill Global Education Holdings, 2009. Chapter 21, Atrial fibrillation. Available at www.accessmedicine.com/content.aspx?aID=3648801 [Accessed 4 January 2014].
3. Gutierrez C, Blanchard DG. Atrial fibrillation: diagnosis and treatment. Am Fam Physician 2011;83:61–68.
4. 2012 Focused update of the ESC guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Eur Heart J 2012;33:2719–47.
5. Rossi S, editor. Tachyarrythmias. In: Australian Medicines Handbook 2013. Adelaide: Australian Medicines Handbook Pty Ltd; 2013.
6. Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med 2002;347:1825–33.
7. Stroke Foundation. National stroke audit acute services. Clinical audit report 2011. Available at strokefoundation.com.au/site/media/National_stroke_audit_acute_services_clinical_audit_report_2011.pdf [Accessed 4 January 2014].
8. NPSMedicinewise. A guide to starting oral anticoagulants in atrial fibrillation. Available at www.nps.org.au/health-professionals/resources-and-tools/decision-and-management-tools/decision-tools/starting-oral-anticoagulants [Accessed 4 January 2014].
9. Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001;285:2864–70.
10. Pisters R, Lane DA, Nieuwlaat R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial

fibrillation: the Euro Heart Survey. Chest 2010;138:1093–100.

11. NPS MedicineWise. Evidence summary on oral anticoagulants and stroke prevention in atrial fibrillation. Available at www.nps.org.au/medicines/heart-blood-and-blood-vessels/anti-clotting-medicines/for-individuals/anticoagulant-medicines/for-health-professionals/evidence-summary/atrial-fibrillation [Accessed 14 January 2014].
12. NPS MedicineWise. Dabigatran (Pradaxa) for stroke prevention in patients with non-valvular atrial fibrillation. Available at www.nps.org.au/publications/health-professional/nps-radar/2011/august-2011/dabigatran-af [Accessed 4 January 2014].
13. NPS MedicineWise. Rivaroxaban (Xarelto) for stroke prevention in non-valvular atrial fibrillation. Available at www.nps.org.au/publications/health-professional/nps-radar/2012/december-2012/rivaroxaban-nvaf [Accessed 4 January 2014].
14. NPS MedicineWise. Apixaban (Eliquis) for stroke prevention in non-valvular atrial fibrillation. Available at www.nps.org.au/publications/health-professional/nps-radar/2013/august-2013/apixaban [Accessed 4 January 2014].
15. Rossi S, editor. Warfarin. In: Australian Medicines Handbook 2013. Adelaide: Australian Medicines Handbook Pty Ltd; 2013. Available at www.amh.net.au/online [Accessed 3 February 2014].
16. Rossi S, editor. Dabagitran. In: Australian Medicines Handbook 2013. Adelaide: Australian Medicines Handbook Pty Ltd; 2013. Available at www.amh.net.au/online [Accessed 3 February 2014].
17. Rossi S, editor. Rivaroxaban. In: Australian Medicines Handbook 2013. Adelaide: Australian Medicines Handbook Pty Ltd; 2013. Available at www.amh.net.au/online [Accessed 3 February 2014].
18. Rossi S, editor. Apixaban. In: Australian Medicines Handbook 2013. Adelaide: Australian Medicines Handbook Pty Ltd; 2013.Australian Medicines Handbook: 2013 [Accessed 3 February 2014].
19. Australian Government Department of Health. PBS: Blood and blood forming organs: Antithrombotic Agents. Dabigatran. Available at www.pbs.gov.au/medicine/item/5054B [Accessed online 15 January 2014].
20. Australian Government Department of Health. PBS: Blood and blood forming organs: Antithrombotic Agents. Rivaroxaban. Available at www.pbs.gov.au/medicine/item/5054B [Accessed online 15 January 2014].
21. Australian Government Department of Health. PBS: Blood and blood forming organs: Antithrombotic Agents. Abixaban. Available at www.pbs.gov.au/medicine/item/5054B [Accessed online 15 January 2014].
22. Queensland Health. Guideline for managing patients on Dabagatran (Pradaxa) Statewide. Version No.: 2.0 Effective from 21/052013. Available at http://www.health.qld.gov.au/qhcss/mapsu/documents/dabigatran_info.pdf [Accessed 15 January 2014].
23. Canadian Agency for Drugs and Technologies in Health. Safety, effectiveness, and cost-effectiveness of new oral anticoagulants compared with warfarin in preventing stroke and other cardiovascular events in patients with atrial fibrillation 2012. Available at www.cadth.ca/media/pdf/NOAC_Therapeutic_Review_final_report.pdf [Accessed 15 January 2014].
24. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139–51.
25. Rossi S, editor. Ischaemic stroke and transient ischaemic attacks. In: Australian Medicines Handbook 2013. Adelaide: Australian Medicines Handbook Pty Ltd; 2013. Available at www.amh.net.au/online [Accessed 3 February 2014].
26. Granger CB, Alexander JH, MacMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981–92.
27. Wallentin L, Lopes RD, Hanna M, et al. Efficacy and safety of apixaban compared with warfarin at different levels of predicted INR control for stroke prevention in atrial fibrillation. Circulation 2013;127:2166–76.
28. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883–91.
29. Heidelbuchel H, Verhamme P, Alings M, et al. EHRA practical guide for use of the new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary 2013. Eur Heart J. 2013;34:2094–2106.
30. Hankey GJ and Eikelboom JW. Dabigatran etexilate: a new oral thrombin Inhibitor. Circulation 2011;123:1436–50.
31. Stangier J, Rathgen K, Stähle H, Mazur D. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate: an open label, parallel group, single-centre study. Clin Pharmacokinet 2010:49:259–268.

CASE 3

ALISON IS SUDDENLY SHORT OF BREATH

Alison, aged 37 years, developed shortness of breath and chest pain this morning. Her past medical history includes only exercise-induced asthma. She has no known medication allergies and takes only the combined oral contraceptive pill and salbutamol as needed. She is married, has two teenage children and works 4 days a week in a garden centre.

QUESTION 1

What questions should you ask about the presenting complaint?

FURTHER INFORMATION

On examination, Alison is obese and can talk in full sentences. Her heart rate is 104 bpm and regular, respiratory rate is 24 breaths per minute, blood pressure 144/90 mmHg, temperature 37.4°C and oxygen saturation 94%. There is no peripheral cyanosis or chest wall tenderness. Chest expansion, percussion, auscultation and groin/leg pulses are all normal. Her legs and ankles seem normal with the exception of varicose veins, of which one on her left calf shows some tracking nodular inflammation. She says she was prescribed antibiotics for it last week but it has become worse.

QUESTION 2

What is Alison's problem most likely to be? Describe the key features, complications and management of this condition.

QUESTION 3

What is the most likely cause of Alison's chest pain and shortness of breath? What tests/investigations would you perform immediately?

QUESTION 4

Would you perform a D-dimer test?

FURTHER INFORMATION

A discharge summary arrives a week later confirming a pulmonary embolism secondary to an occult DVT in the superficial femoral vein and informs you of Alison's commencement on warfarin.

QUESTION 5

What is significant about the term 'superficial' femoral vein?

QUESTION 6

How does anticoagulation treatment differ for DVT and superficial venous thrombosis?

FURTHER INFORMATION

Alison returns to you with a series of questions.

QUESTION 7

Alison asks, 'What caused it? Can I do anything to stop it happening again?' What would you advise her?

QUESTION 8

Alison asks, 'This warfarin testing and dose changing is a bit much. Can't I just take aspirin?' How would you respond?

QUESTION 9

Alison asks what you think about a 'new' drug. What would you tell her?

QUESTION 10

Alison wants to know why she has to wear a stocking and for how long. How do you answer these questions?

CASE 3 ANSWERS

ANSWER 1

Alison should be asked about any precipitating events that she believes may have led to her current situation. She should be asked to clarify what she means by shortness of breath. You should also ask questions about any associated pain that she may be experiencing and about any other cardiac and/or respiratory symptoms (palpitations, syncope, orthopnoea, claudication, wheeze, haemoptysis or cough) and enquire about symptoms, risk factors and family history of serious conditions, including:

- infection (fever, contact with others, birds, moulds, recent travel, etc.)
- malignancy (weight loss, night sweats, smoking, industrial exposure)
- cardiac disease (hypertension, cholesterol, diabetes, smoking)
- pulmonary embolus (recent stasis/surgery, malignancy, prior deep venous thrombosis (DVT) irritable bowel disease, pregnancy, smoking, oestrogen-based medication).[1]

Alison confirms no precipitating event. The shortness of breath is constant, consisting of short breaths accompanied by right lateral, pleuritic pain that worsens with exercise and is not alleviated by anything. She denies any other symptoms, any contact with others with the same symptoms and any injury, surgery, travel or immobility. There is no significant family history. She works with potting mixes. She ceased smoking 2 years ago. Her blood pressure is usually normal and she has never had her cholesterol or blood sugar tested.

ANSWER 2

Alison's problem is most likely superficial venous thrombosis (thrombophlebitis), which is thrombus formation in the superficial venous system. It is often associated with varicose veins and presents with tracking inflammation (e.g. redness, swelling, heat) that can be confused with cellulitis. It is not infective, so unless there has been some recent instrumentation or injection, antibiotics are not indicated. Intravenous cannulation, pregnancy, malignancy and other causes of venous stasis or trauma have been associated with presentations of superficial venous thrombophlebitis.[2]

Superficial venous thrombophlebitis is usually a self-limiting condition.[2] The main complication is a 10% chance of the thrombus extending, about half of which will 'grow' into the deep vein system. Additionally, up to 25% of patients may present with occult DVT.[3]

Management of spontaneous superficial thrombophlebitis requires low molecular weight heparin (LMWH) (e.g. enoxaparin 40 mg subcutaneous daily) for 4 weeks, unless the bleeding risk is high, in which case surveillance is recommended; 2–3 duplex ultrasounds over several weeks.[2,3] Seek occult DVT with duplex ultrasound.[3]

Use of LMWH does not require any laboratory monitoring and LMWHs should be used cautiously in those with renal impairment.[4]

Baseline haemoglobin, platelets, APTT, INR and creatinine should be checked before starting treatment.[4]

ANSWER 3

Pulmonary embolism seems most likely. Confirm the probability with a Well's score for pulmonary embolism and exclude ischaemia with an ECG (which could also suggest pulmonary embolism: S1 Q3 T3 ±right heart strain).

A Wells score is a validated scoring system of seven criteria and was developed in the late 1990s to clinically predict the likelihood of PE (*Table 1*). Using the table below, you can calculate Alison's Wells score.

Table 1. Wells score for clinically predicting the probability of pulmonary embolism[5]

Variable	Score
Previous pulmonary embolism or DVT	1.5
Tachycardia: >100 bpm	1.5
Recent surgery or immobilisation (within previous 4 weeks)	1.5
Clinical symptoms of DVT	3
Alternative diagnosis is less likely than pulmonary embolism	3
Haemoptysis	1
Cancer: palliative, current treatment or such in last 6 months	1
Risk stratification: low 0–1; intermediate: 2–6; high: 7 or more	
Her Wells score is 4.5 (tachycardia, alternative diagnosis less likely).	

ANSWER 4

A D-dimer test is not required in this instance. A D-dimer test is needed if the diagnosis is doubtful, in which case a negative test plus a Wells score of ≤4 excludes pulmonary embolism.[6]

High clinical suspicion of pulmonary embolism requires immediate inpatient evaluation and guidelines recommend starting appropriate treatment while awaiting test results.[4]

ANSWER 5

Despite its name, it is not a superficial vein. It is a deep vein and acute thrombosis of this vessel is potentially life threatening. Any thrombus therein should be treated with an anticoagulant as per DVT.[3,7]

ANSWER 6

Management of spontaneous superficial thrombophlebitis requires short-term anticoagulation as discussed earlier, whereas DVT requires longer anticoagulation treatment. Three months of anticoagulation is required for an unprovoked distal DVT (below the popliteal vein) or for DVT provoked by a major transient risk factor (e.g. surgery, trauma, immobilisation for more than 3 days, pregnancy or postpartum management, oral contraceptive or hormone replacement therapy). Six months is required after any

first unprovoked proximal DVT or pulmonary embolism. Indefinite anticoagulant treatment is needed for any unprovoked recurrence or any unprovoked DVT with active risk factors: cancer, thrombophilia or antiphospholipid antibody syndrome.[2]

ANSWER 7

You explain that her varicose veins together with her use of the oral contraceptive pill have most likely contributed to her current problems. She can minimise the chance of recurrence by avoiding provoking factors as listed above. Also, because the risk of recurrent superficial thrombosis is high, and varicose veins have been a contributing factor, she should consider treatment.[3]

ANSWER 8

The guidelines do not recommend aspirin for prophylaxis of venous thromboembolism, as a range of more effective therapies are available.[4]

Aspirin prevents platelet aggregation, which is how clots form in arteries. However, in veins, clots are formed by clotting factors, not by platelet aggregation. Aspirin, therefore, is ineffective and warfarin is required.[8]

ANSWER 9

Rivaroxaban has recently been listed on the PBS as a streamlined authority for confirmed acute pulmonary embolism (for use in the initial treatment phase) at a dosage of 15 mg twice daily for 3 weeks, then 20 mg daily thereafter.[9,10]

You explain that, unlike for warfarin, there is no validated test for measuring coagulation levels and no antidote for acute bleeding for rivaroxaban. You download a flyer for patients (rivaroxaban) consumer medicine information (CMI) leaflet. She says she'll think about it.

ANSWER 10

You discuss post-thrombotic syndrome, which may include pain, swelling, varicose eczema, skin thickening and staining, which occurs after 60% of DVTs. The incidence of these problems can be halved by wearing a graduated compression stocking.[8] Wearing a knee high stocking with 30–40 mm Hg pressure at the ankle for 18 months is recommended. Stockings should be fitted by an experienced professional, because of the pressure differences.[2]

REFERENCES

1. Murtagh J. General Practice 5th ed. North Ryde: McGraw-Hill; 2011.
2. Treatment of deep vein thrombosis and pulmonary embolism. In: eTG [Internet]. Melbourne. Therapeutic Guidelines Limited; January 2014 [Accessed Jan13 2014].
3. Robinsons, D. Calf vein thrombosis and superficial venous thrombosis: Advice on management. Medicine Today 2013;14:18–24.
4. Rossi S, editor. Treatment of venous thromboembolism. In: Australian Medicines Handbook 2013. Adelaide: Australian Medicines Handbook Pty Ltd; 2013.Australian Medicines Handbook. Available at www.amh.net.au [Accessed 20 January 2014].
5. Wells P, Andersons M, Rodger M, et al. Derivation of a simple clinical model to categorise patients' probability of pulmonary embolism: increasing the model's utility with the simpliRED D-Dimer. Thromb Haem 2000;83:358–19.
6. Geersing GJ, Erkens PM, Lucassen WA, et al. Safe exclusion of pulmonary embolism using the Wells rule and qualitative D-dimer testing in primary care: prospective cohort study. BMJ 2012;345:e6564.
7. Bundens WP, Bergan JJ, Halasz NA, Murray J, Drehobl M. The superficial femoral vein. A potentially lethal misnomer. JAMA 1995;274:1296–98.
8. Flecknoe-Brown S. How to treat: clotting conditions. In: How to Treat Yearbook 2010 pp295–30.
9. Australian Government Department of Health. Pharmaceutical Benefits Scheme. Available at www.pbs.gov.au/medicine/item/2160Q [Accessed 20 January 2014].
10. National Prescribing Service: Anticoagulant listings 2013. Available at www.nps.org.au/medicines/heart-blood-and-blood-vessels/anti-clotting-medicines/for-individuals/anticoagulant-medicines/for-health-professionals/decision-tools/anticoagulants-listings [Accessed 31 January 2014].

RESOURCES FOR PATIENTS

- Xarelto: Consumer medicine information. Available at www.nps.org.au/__data/cmi_pdfs/CMR09333.pdf [Accessed 20 January 2014].

CASE 4

JOHN HAS HIGH CHOLESTEROL

John is a secondary school vice principal aged 45 years and attends your practice after a health check at work. He says that he was told to see his doctor because his cholesterol was too high and that his blood pressure was borderline. He was advised that he would need treatment.

His health check showed the following:

- Total cholesterol (TC) 6.8 mmol/l,
- Low density lipoprotein (LDL) 5.0 mmol/L
- High density lipoprotein (HDL) 1.0 mmol/L
- Triglycerides (TG) 2.1 mmol/L
- BMI 26 m^2/kg
- Blood pressure (BP) 145/85 mmHg.

He is a non-smoker. He says that he won't take any tablets because he feels perfectly well.

QUESTION 1

How would you assess John's current cardiovascular risk?

FURTHER INFORMATION

John's current cardiovascular risk using the Australian Absolute Cardiovascular Risk Calculator is assessed as being low (6%) for a cardiovascular event in the next 5 years. John accepts that his lipid levels are too high but says he wants to 'fix' them naturally. He has been told that he can achieve the same benefit as those achievable with medication by eating more fish, adopting a Mediterranean diet and exercising more.

QUESTION 2

What advice would you give John about his proposed approach? What further advice and/or medication would you give him in view of his stated intentions and current risk profile?

FURTHER INFORMATION

John returns for a check up after working at a country school for 5 years. He is now 50 years old, overweight (BMI 29) and his BP is 155/95 mmHg. His recent total cholesterol was 6.7 mmol/L, LDL 4.8 mmol/L, HDL 0.9 mmol/L, TGs 2.5 mmol/L.

QUESTION 3

How would you assess, advise and manage John at this point?

FURTHER INFORMATION

John returns after 6 months to get his latest blood test results. His TC is 6.6 mmol/L, LDL 4.9 mmol/, HDL 0.9 mmol/L, TG 2.3 mmol/L. His BP is 160/95 mmHg and home readings have ranged between 145/85 and 180/100 mmHg.

QUESTION 4

What options would you consider in managing John's cardiovascular risk at this time?

FURTHER INFORMATION

John returns for a repeat script for his blood pressure medication 6 months after the last visit and explains that he is no longer taking his statin after having watched a TV show suggesting these tablets are potentially harmful and are not necessary.

QUESTION 5

What advice would you give John at this point? How would you discuss the message described in the TV show?

FURTHER INFORMATION

Despite listening to your explanation and acknowledging that there needs to be a trade-off between benefit and risk, he explains that he prefers to stop taking statin tablets for the time being. John continues to see you for BP medication every 6–7 months but comes to see you 2 years later following discharge from hospital after a non-ST segment elevation myocardial infarction (NSTEMI). He is annoyed that his hospital cardiologist insisted that he has no option now but to take a statin and that he did not seem interested in John's point of view, that statins were more dangerous than helpful in his case.

QUESTION 6

What advice would you give John? How would you advise John in relation to his current cardiovascular risk and need, if any, for medication?

CASE 4 ANSWERS

ANSWER 1

Current guidelines support assessment and management of people like John (i.e. without known history of CVD; primary prevention) on the basis of their calculated absolute cardiovascular risk. The person's calculated risk informs management decisions and clarifies the role of pharmacotherapy.[1]

Dyslipidaemia is only one of several risk factors for CVD. Although there is good evidence to support the use of statins to reduce cardiovascular risk, it is essential to assess absolute cardiovascular risk to appropriately determine overall risk for individual patients[2,3] before making management decisions. Assessment of risk, taking into account multiple risk factors (absolute cardiovascular risk), is more accurate than consideration of single risk factors (e.g. lipid levels), as the cumulative effect of multiple risk factors is believed to be additive or synergistic.[2] More than 90% of adult Australians have one modifiable risk factor for cardiovascular disease and 64% have three or more.[4] When it comes to reducing overall cardiovascular risk, a moderate reduction in several risk factors is more effective than a major reduction in just one risk factor.[1]

In patients not clearly at high risk, it is recommended that their absolute cardiovascular risk is calculated using an appropriate tool such as Australian cardiovascular risk charts provided in the Australian National Vascular Guidelines.[5–7] Pharmacotherapy is not required by all patients. A person's calculated level of risk determines whether pharmacotherapy is needed or not. For those at high risk, guidelines recommend simultaneous treatment with lipid-lowering and BP-lowering medications, unless contraindicated or clinically not appropriate. For those at moderate or low cardiovascular risk, medication (e.g. statins) is not routinely recommended.[8] Lifestyle advice, including support on diet, physical activity and smoking

cessation, should be offered to all patients irrespective of their level of cardiovascular risk.[8] In summary all management decisions should be based on absolute cardiovascular risk.[5].

The Australian cardiovascular risk charts are based on the Framingham Risk Equation and take into account gender, age, BP, smoking status, TC and HDL, diabetes status and left ventricular hypertrophy (LVH) on ECG. The calculator gives a measure of estimated numerical risk of a cardiovascular event within the next 5 years as high (>16%), moderate (10–15%) and low (<10%).

While a risk calculation can help with management decisions, it is still necessary to undertake a full cardiovascular assessment taking into account additional modifiable and non-modifiable risk factors and other related conditions. Fasting blood glucose (FBG) should also be measured to exclude diabetes. Other factors to consider in this assessment include central obesity, waist circumference and BMI, poor nutrition, sedentary lifestyle and excessive alcohol intake, social history (including cultural identity and ethnicity e.g. Aboriginal and Torres Strait Islander, Maori and Pacific Islander, South Asian, Middle Eastern peoples and those of lower socioeconomic status). Related conditions, such as chronic kidney disease (albuminuria with or without proteinuria and/or reduced eGFR), familial hypercholesterolaemia, evidence of AF and mental health issues such as stress, also need to be considered.[1]

It is important to remember that certain groups can have their risk underestimated with a risk calculator and in these patients a calculation should be seen as minimum risk (e.g. predictive value has not been assessed in overweight/obese adults), while others do not do not need their risk calculated as they are known to be at high risk of cardiovascular disease (e.g. people with diabetes over 60 years).[1]

ANSWER 2

Lifestyle changes involving diet and increasing physical activity have been shown to effectively lower disease burden, especially in relation to obesity and future heart disease and diabetes.[1] It is, however, difficult to undertake randomised controlled trials of lifestyle factors when many are related to each other (e.g. diet and exercise or smoking status), without introducing inherent bias. Randomised controlled trials addressing such complex interrelated factors are more difficult to undertake than those investigating pharmacological interventions. Hence, most of the data relating to the effect of lifestyle interventions is from cohort or observational studies.

A 2013 Cochrane review[9] reported that giving people dietary advice, such as reducing consumption of fat, saturated fatty acids, cholesterol and salt, and increasing the consumption of fruit, vegetables, polyunsaturated and monosaturated fatty acids, reduced total and LDL cholesterol and BP, without any statistical significant changes to HDL or TGs.

There is conflicting evidence about the benefits of regularly consuming fish or fish oil (omega-3 fatty acid) supplements. Omega-3 fatty acid supplements reduce TGs by 20–30% and are recommended for treating hypertriglyceridaemia.[5] Lower rates of coronary events, sudden death and total mortality have been reported to be associated with higher fish intake[10–12] but a systematic review of 48 randomised controlled trials showed no benefit in patients with existing CHD.[13] Current guidelines based on population studies recommend fish consumption 2–3 times per week as part of an appropriate balanced diet.[2,5]

The Mediterranean diet involves consumption of high levels of olive oil, legumes, unrefined cereals, fruits, vegetables, moderate-to-high consumption of fish, moderate consumption of dairy products and wine and low consumption of meat and meat products.[14] A 2008 systematic review of 12 observational studies found adherence to a Mediterranean diet is associated with reduced cardiovascular risk and total mortality.[15].

Several meta-analyses have shown an inverse relationship between physical activity and the risk of a cardiovascular event and all-cause mortality.[16–19] Two and a half hours of moderate intense activity per week is associated with a 19% reduction in mortality risk, compared to no activity[20]. Dose–response relationships between exercise duration over a week or exercise intensity on the one hand and mortality risk, have been demonstrated and the greatest benefits are seen in those moving from no activity to low activity.[16,17,20,21] Benefits from increasing physical activity levels can be attained for those starting with minimal activity levels, as well as those increasing from mild or moderate existing activity levels.[6]

A number of randomised controlled trials and meta-analyses show significant benefits of physical activity on a number of cardiovascular risk factors,[22–26] including reducing LDL and TGs, increasing HDL[24] and insulin sensitivity,[26] reducing body fat[23,25] and lowering BP.[22–24]ßß

It is appropriate to recommend that all patients with high LDL undertake lifestyle modifications such as aerobic exercise, a healthy diet and weight loss for overweight patients.

ANSWER 3

John's risk should be recalculated and his calculated risk should inform the development of a management plan for him if required.[1] An ECG should be done to exclude CAD and ILVH. FBG should also be reassessed.

Using the risk calculator, John is now at medium risk (11%) of a cardiovascular event over the next 5 years. Lipid-lowering or BP-lowering therapy is not routinely recommended for patients at moderate cardiovascular risk; however, medication may be appropriate in some circumstances.[1]

Initial recommendations to John should be to reinforce the importance of an appropriate diet and increasing physical activity.

BP-lowering or lipid-lowering medication might be considered if 3–6 months of appropriate behavioural risk factor modification does not reduce his absolute cardiovascular risk or if his BP remains persistently above 160/100 mmHg, he has a family history of premature CVD or he is in a specific population group in which the Framingham Risk Equation underestimates his risk. These groups include Aboriginal and Torres Strait Islander people, certain ethnic groups, younger people with diabetes, overweight or obese people and people of lower socioeconomic status. In these situations, the calculated risk should be treated as a minimum estimate that is then adjusted according to clinical judgement.[1]

ANSWER 4

John is still at moderate cardiovascular risk but now qualifies for PBS-reimbursed statin therapy on the basis of his low HDL and high TC.[1] He is significantly overweight, which is known to underestimate absolute cardiovascular risk[1] and his BP is now consistently elevated despite appropriate lifestyle intervention. The case for commencing low dose statin therapy is now a stronger one. However, ultimately the decision to commence a statin should be made by the patient after appropriate discussion of the risks and benefits of statin therapy.

Statins reduce the risk of cardiovascular events and death in people with increased cardiovascular risk regardless of initial lipid levels. However, the benefits of statin therapy are greatest for those at highest risk.[27,28] The addition of statin therapy for primary prevention (of cardiovascular disease) at this time would be based on the 20–30% expected reduction in CVD events seen in most clinical trials of statin therapy rather than aiming at a specific LDL level.[27,28] Although statins differ in potency, no one statin has been shown to have a clear proven advantage on the basis of outcomes data.[29] The choice of statin, starting and maximum doses and target lipid levels should be individualised on the basis of whether use is for primary or secondary prevention and the degree of patient cardiovascular risk.

The use of non-statin lipid lowering therapy for primary prevention in a case such as this is not generally recommended given the lack of supporting trial data and the concern about increased non-cardiovascular mortality shown in several trials looking at non-statin lipid lowering therapy in primary prevention.[30-33]

Regardless of the decision about lipid-lowering therapy, John should be commenced on BP-lowering therapy at this time given his persistently elevated BP readings despite his best efforts at lifestyle modification.

John's absolute cardiovascular risk should be reassessed in 6–12 months time.

ANSWER 5

It is important to review the risks and benefits of statin therapy with John, in particular, discussing the side effects that were highlighted in the TV program. However, if after appropriate discussion, John is still not willing to resume statin therapy, and given that his cardiovascular risk is only moderate, it would certainly be appropriate to accept his decision as a reasonable one.

It would be important to emphasise again that cardiovascular risk is multifactorial and to remind him of the benefits of lifestyle modification and of the importance of continuing to take his BP medication. It would be appropriate to review his cardiovascular risk again in 6–12 months time.

ANSWER 6

Absolute cardiovascular risk assessment identifies those at risk without overt disease. It is not necessary for certain groups already known to be at high risk of CVD.[1] Such groups are those with diabetes over 60 years of age or with microalbuminuria; moderate or severe chronic kidney disease (CKD); previous diagnosis of familial hypercholesterolaemia, systolic BP ≥180 mmHg, or diastolic ≥110 mmHg; serum TC >7.5 mmol/L or Aboriginal and Torres Strait Islander peoples over 74 years old.

Now that John has had a cardiovascular event, he is and will always remain at high risk with at least a >15% 5-year risk of a further cardiovascular event. Patients, like John who have had a cardiovascular event, have existing CVD and need to managed according to secondary prevention guidelines.[8] The optimal management of John's cardiovascular risk now includes aggressive lipid-lowering and BP-lowering treatment, aspirin therapy and appropriate lifestyle modification.[34] It is important to carefully explain the evidence supporting such treatment as well as the potential side effects of treatment. If after adequate explanation of the appropriate evidence John still decides to refuse statin treatment, discussing alternative lipid-lowering medication as secondary prevention would be worth trying. If John then made an informed decision to refuse any lipid-lowering medication, a summary of the discussion and a note that John understands the risks of not taking such treatment should be recorded in his medical record. John should continue to be seen every 3–6 monthly to ensure his BP is managed at target levels, and he should continue to receive advice as to the importance of appropriate diet and activity levels for controlling his risk.

REFERENCES

1. National Vascular Disease Prevention Alliance. Guidelines for the management of absolute cardiovascular disease risk. 2012. Available at strokefoundation.com.au/site/media/AbsoluteCVD_GL_webready.pdf [Accessed 19 January 2014].
2. Tonkin A, Barter P, Best J, et al. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand. Position statement on lipid management 2005. Heart Lung Circ 2005;14:275–91.
3. Cooper A, Nherera L, Calvert N, et al. Clinical Guidelines and Evidence Review for Lipid Modification: cardiovascular risk assessment and the primary and secondary prevention of cardiovascular disease (revised March 2010). London: National Collaborating Centre for Primary Care and Royal College of General Practitioners, 2008.
4. Australian Institute of Health and Welfare 2011. Health determinants, the key to preventing chronic disease. Cat No. PHE 157. Canberra: AIHW.
5. eTG complete [online]. Therapeutic Guidelines: Cardiovascular. Melbourne: 2012. Available at online.tg.org.au/complete/desktop/index.htm [Accessed 19 January 2014].
6. National Vascular Disease Prevention Alliance (NVDPA) absolute CVD risk calculator: Available at www.cvdcheck.org.au [Accessed 19 January 2014].
7. National Vascular Disease Prevention Alliance (NVDPA) absolute CVD risk charts: Available at www.heartfoundation.org.au/SiteCollectionDocuments/aust-cardiovascular-risk-charts.pdf [Accessed 19 January 2014].
8. National Heart Foundation. Absolute cardiovascular disease risk assessment. Available at www.heartfoundation.org.au/SiteCollectionDocuments/absolute-risk-assessement.pdf [Accessed 31 January 2014].
9. Rees K, Dyakova M, Wilson N, Ward K, Thorogood M, Brunner E. Dietary advice for reducing cardiovascular risk. Cochrane Database Syst Rev 2013 12:CD002128. Epub 2013 Dec 6. Available at www.ncbi.nlm.nih.gov/pubmed/23543514 [Accessed 19 January 2014].
10. Bouzan C, Cohen JT, Connor WE, Kris-Etherton PM, Gray GM, Konig A, et al. A quantitative analysis of fish consumption and stroke risk. Am J Prev Med 2005 Nov;29:347–52.

11. He K, Song Y, Daviglus ML, et al. Accumulated evidence on fish consumption and coronary heart disease mortality: a meta-analysis of cohort studies. Circulation. 2004;109:2705–11.
12. Wang C, Harris WS, Chung M, et al. n-3 Fatty acids from fish or fish-oil supplements, but not alpha-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: a systematic review. Am J Clin Nutr 2006;84:5–17.
13. Hooper L, Thompson RL, Harrison RA, et al. Risks and benefits of omega 3 fats for mortality, cardiovascular disease, and cancer: systematic review. BMJ 2006;332:752–60.
14. de Lorgeril M, Salen P, Martin JL, et al. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. Circulation 1999;99:779–85.
15. Sofi F, Cesari F, Abbate R, Gensini GF, Casini A. Adherence to Mediterranean diet and health status: meta-analysis. BMJ 2008;337:a1344.
16. Hamer M, Chida Y. Walking and primary prevention: a meta-analysis of prospective cohort studies. Br J Sports Med 2008;42:238–43.
17. Lollgen H, Bockenhoff A, Knapp G. Physical activity and all-cause mortality: an updated meta-analysis with different intensity categories. Int J Sports Med 2009;30:213–24.
18. Nocon M, Hiemann T, Muller-Riemenschneider F, Thalau F, Roll S, Willich SN. Association of physical activity with all-cause and cardiovascular mortality: a systematic review and meta-analysis. Eur J Cardiovasc Prev Rehabil 2008;15:239–46.
19. Shiroma EJ, Lee IM. Physical activity and cardiovascular health: lessons learned from epidemiological studies across age, gender, and race/ethnicity. Circulation 2010;122:743–52.
20. Woodcock J, Franco OH, Orsini N, Roberts I. Non-vigorous physical activity and all-cause mortality: systematic review and meta-analysis of cohort studies. Int J Epidemiol 2011;40:121–38.
21. Hu G, Tuomilehto J, Silventoinen K, Barengo N, Jousilahti P. Joint effects of physical activity, body mass index, waist circumference and waist-to-hip ratio with the risk of cardiovascular disease among middle-aged Finnish men and women. Eur Heart J 2004;25:2212–19.
22. Pal S, Cheng C, Egger G, Binns C, Donovan R. Using pedometers to increase physical activity in overweight and obese women: a pilot study. BMC Public Health 2009;9:309.
23. Pedersen MT, Blangsted AK, Andersen LL, Jorgensen MB, Hansen EA, Sjogaard G. The effect of worksite physical activity intervention on physical capacity, health, and productivity: a 1-year randomized controlled trial. J Occup Environ Med 2009;51:759–70.
24. Carroll S, Dudfield M. What is the relationship between exercise and metabolic abnormalities? A review of the metabolic syndrome. Sports Med 2004;34:371–418.
25. Orozco LJ, Buchleitner AM, Gimenez-Perez G, Roque IFM, Richter B, Mauricio D. Exercise or exercise and diet for preventing type 2 diabetes mellitus. Cochrane Database Syst Rev 2008;3:CD003054.
26. Thomas DE, Elliott EJ, Naughton GA. Exercise for type 2 diabetes mellitus. Cochrane Database Syst Rev 2006;3:CD002968.
27. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366:1267–78.
28. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;360:7–22.
29. NPS News. Managing lipids – reducing cardiovascular disease risk. Feb 2011 (Modified March 2011). Available at www.nps.org.au/publications/health-professional/nps-news/2011/lipids [Accessed 21 January 2014].
30. A cooperative trial in the primary prevention of ischaemic heart disease using clofibrate. Report from the Committee of Principal Investigators. Br Heart J 1978;40:1069.
31. WHO cooperative trial on primary prevention of ischaemic heart disease using clofibrate to lower serum cholesterol: mortality follow-up. Report of the Committee of Principal Investigators. Lancet 1980;2:379.
32. The Lipid Research Clinics Coronary Primary Prevention Trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. JAMA 1984;251:365.
33. Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. N Engl J Med 1987;317:1237.
34. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand. Reducing risk in heart disease: an expert guide to clinical practice for secondary prevention of coronary heart disease. Melbourne: National Heart Foundation of Australia, 2012. Available at www.heartfoundation.org.au/SiteCollectionDocuments/Reducing-risk-in-heart-disease.pdf [Accessed online 22 January 2014].

CASE 5

SUSAN'S HUSBAND DIED SUDDENLY AFTER EXERCISE

A hospital doctor contacts you to notify you of the sudden death of one of your patients, Graham, aged 30 years, whom you had previously seen intermittently. His last visit was 2 months ago, when you prescribed oral antibiotics for bronchitis. You also treat his wife, Susan, aged 28 years, and their two children aged 2 and 4 years.

You review Graham's notes, which document that he was a non-smoker, on no regular medications and had normal blood pressure. He had no heart murmurs.

You notice that Susan has booked an appointment to see you later that day.

QUESTION 1

What resources are available to families of sudden cardiac death (SCD)?

FURTHER INFORMATION

Susan presents for her appointment and tells you that Graham had been well in the days leading up to his usual weekend touch football match but he collapsed after the game. His teammates called an ambulance and commenced cardiopulmonary resuscitation; however, he was unable to be resuscitated. Susan was told that an autopsy would be done on Graham and that she would be notified of the results.

QUESTION 2

What further history could be relevant?

QUESTION 3

What are the causes of SCD in the young?

FURTHER INFORMATION

Guidelines endorsed by the Royal Australasian College of Pathologists have been developed for autopsies performed on individuals who have died suddenly at a young age. These guidelines recommend a toxicology screen, tests to exclude non-cardiac causes of death (e.g. aortic aneurysm, cerebral haemorrhage and pulmonary thromboembolism), and macroscopic/microscopic examination of the heart. If an inherited cause of death is identified or if the post-mortem is negative (no cause of death identified), tissue or blood should be collected for DNA extraction.[1]

QUESTION 4

What advice should you give to family members?

FURTHER INFORMATION

Subsequently, Susan receives the autopsy report, which indicates that the cause of death was hypertrophic cardiomyopathy. Susan tells you that she was informed that blood was stored for potential genetic testing.

QUESTION 5

How long should clinical screening in relatives be continued?

QUESTION 6

What is the role of genetic testing?

CASE 5 ANSWERS

ANSWER 1

There are many resources available to assist families with SCD. The Australian Genetic Heart Disease Registry has a link dedicated to SCD where comprehensive patient information sheets are available, and links to various support groups are provided (see Resources for Patients below).

ANSWER 2

This is clearly a difficult time for Susan and her children. Your approach will be dependent on their reaction to the recent, sudden, unexpected loss of their husband/father. Susan will want to know why this has happened and whether other family members are at risk.

The Trans-Tasman response Against Sudden death in the Young (TRAGEDY) initiative emphasises the importance of obtaining detailed medical histories in cases of sudden death in young people.[1] At some point, therefore, it is important to take a further history, given that inherited heart disease is a prominent cause of SCD in the young. This will include asking further questions about the circumstances surrounding the event, the amount of exercise that Graham undertook, and whether Graham had any previous history of syncope, palpitations, chest pain or exercise intolerance. A family history of SCD, drownings, epilepsy, recurrent syncope or premature vascular disease is also relevant. You should ask whether Graham was taking any medications, including over-the-counter drugs. You should also ascertain whether any prior cardiac or neurological investigations had been performed for Graham e.g. 12-lead ECG, echocardiogram, stress test, electroencephalogram (EEG), computerised tomography (CT) or magnetic resonance imaging (MRI) of the brain, fasting lipids.

ANSWER 3

In the general population, the most common cause of SCD is CAD; however, it accounts for a smaller proportion of sudden deaths in younger individuals (aged <40 years).[2]

The causes of sudden death can be broadly categorised into structural heart diseases or non-structural diseases (also referred to as primary arrhythmogenic disorders).[8] Structural diseases include CAD, cardiomyopathies (e.g. hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy), myocarditis and congenital heart disease. Primary arrhythmogenic diseases include long QT syndrome, catecholaminergic polymorphic ventricular tachycardia and Brugada syndrome.

The post-mortem has a high probability of identifying structural causes of SCD.[3,4] Hypertrophic cardiomyopathy is one of the most common causes of SCD in the young, especially when related to exercise.[5] However, in 30% of SCD cases occurring in people aged 35 years or younger, no cause of death is identified at postmortem;[3,4] at least 40% of these cases are attributable

to inherited primary arrhythmogenic disorders that cannot be diagnosed at autopsy.[6–8]

ANSWER 4

Many of the causes of SCD in the young (including hypertrophic cardiomyopathy) are inherited, usually as an autosomal dominant condition.[3] Therefore, first-degree relatives (i.e. children, siblings and parents) have a 50% risk of carrying the gene mutation and should be referred to a cardiologist for clinical evaluation. This should occur if the post-mortem either identifies an inherited cardiac disease (e.g. hypertrophic cardiomyopathy) or if the post-mortem is negative (i.e. no cause of death is identified). First-degree relatives should also be referred for clinical assessment if no autopsy was performed. One should consider referring families where no cause of death has been identified at autopsy to specialised centres that run multidisciplinary clinics that coordinate both the cardiological and genetic investigation of families.[6,7]

Clinical screening of family members generally involves,[7] as a minimum:

- ECG
- Transthoracic echocardiogram.

A diagnosis of inherited heart disease in a relative may allow early lifestyle modification, avoidance of specific drugs that may precipitate arrhythmias, and prophylactic treatment to reduce their future risk of SCD.[6,7] It may also identify other at-risk relatives who should undergo clinical evaluation.

You advise Susan that Graham's parents and siblings should undergo clinical screening by a cardiologist. You refer Susan's children to a paediatric cardiologist.

ANSWER 5

Inherited heart diseases are not expressed at a particular age; therefore, depending on the age of the relative, ongoing clinical screening should be performed every 1–5 years. This should be guided by the cardiologist. Guidelines are available on the Cardiac Society of Australia and New Zealand website (see Resources for Doctors below).

ANSWER 6

Genetic testing may have an important role in the investigation of SCD families.[2,7] For a number of inherited cardiac diseases, including hypertrophic cardiomyopathy, genetic testing is now part of standard clinical practice.[2] In approximately 50–60% of hypertrophic cardiomyopathy patients, a causative mutation can be identified.[2] This allows predictive genetic testing in at-risk relatives to determine whether or not they carry the mutation. Carriers require ongoing follow-up;[6,7] however, non-carriers can be discharged from long-term clinical screening and reassured that they are not at increased risk of developing hypertrophic cardiomyopathy.

Genetic evaluation may also be considered in families where no cause of death is identified at autopsy,[2,6–8] depending on the circumstances of the SCD, the number of SCDs occurring in that family, and the outcome of clinical screening performed in relatives. A combined approach to clinical screening in relatives and genetic testing can identify an inherited cardiac disease in up to 30–40% of families.[6–9]

There are a number of genetic testing services available in Australia, including centres that have a special interest in cardiac genetics (see Resources for Doctors below). They are composed of multidisciplinary teams (including cardiologists, clinical geneticists and genetic counsellors) and provide genetic counselling regarding the risk of other family members developing inherited cardiac disease and the potential impact of genetic testing on future employment, recreation, insurance and reproduction.

You refer Susan to a clinical genetics service to consider whether genetic testing for hypertrophic cardiomyopathy could be considered for her family. Blood had been collected from Graham at post-mortem and DNA was extracted and stored. As next of kin, Susan can authorise genetic testing of the DNA samples. This testing has a 50–60% chance of finding the causative mutation. Identification of a mutation could warrant predictive genetic testing of other family members to determine whether or not they are carriers.

REFERENCES

1. Skinner JR, Duflou JA, et al. Reducing sudden death in young people in Australia and New Zealand: the TRAGADY initiative. Med J Aust 2008;189:539–40.
2. Ackerman MJ, Priori SG, Willems S, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Heart Rhythm 2011;8:1308–39.
3. Doolan A, Langlois N, Semsarian C. Causes of sudden cardiac death in young Australians. Med J Aust 2004;180:110–12.
4. Puranik R, Chow CK, Duflou JA, Kilborn MJ, McGuire MA. Sudden death in the young. Heart Rhythm 2005;2:1277–82.
5. Maron BJ. Sudden death in young athletes. N Engl J Med 2003;349:1064–75.
6. Nunn LM, Lambiase PD. Genetics and cardiovascular disease – causes and prevention of unexpected sudden adult death: the role of the SADS clinic. Heart 2011;97:1122–27.
7. Vohra J, Skinner J, Semsarian C. Cardiac genetic investigation of young sudden unexplained death and resuscitated out of hospital cardiac arrest. Heart Lung Circ 2011;20:746–50.
8. Semsarian C, Hamilton RM. Key role of the molecular autopsy in sudden unexpected death. Heart Rhythm 2012;9:145–50.
9. Skinner JR, Crawford J, Smith W, et al. Prospective, population-based long QT molecular autopsy study of postmortem negative sudden death in 1 to 40 year olds. Heart Rhythm 2011;8:412–19.

RESOURCES FOR DOCTORS

- SCD clinical screening guidelines are available on the Cardiac Society of Australia and New Zealand website (www.csanz.edu.au/documents/guidelines/clinical_practice/Hyertrophic_Cardiomyopathy.pdf).
- Genetic testing services available in Australia including centres with a special interest in cardiac genetics (www.heartregistry.org.au/patients-families/cardiac-genetic-services/).

RESOURCES FOR PATIENTS

- The Australian Genetic Heart Disease Registry has a link dedicated to SCD. Comprehensive patient information sheets are available at www.heartregistry.org.au
- Sudden Arrhythmic Death Syndromes Australia (SADS), www.sads.org.au
- NALAG Centre for Loss and Grief (Australia), www.nalag.org.au
- Lifeline Australia, www.lifeline.org.au

Heart health

In order to qualify for 6 Category 2 points for the QI&CPD activity associated with this unit:

- read and complete the unit of *check* in hard copy or online at the *gplearning* website at http://gplearning.racgp.org.au
- log into the *gplearning* website at http://gplearning.racgp.org.au and answer the following 10 multiple choice questions (MCQs) online
- complete the online evaluation.

If you are not an RACGP member, please contact the *gplearning* helpdesk on 1800 284 789 to register in the first instance. You will be provided with a username and password that will enable you access to the test.

The expected time to complete this activity is 3 hours.

Do not send answers to the MCQs into the *check* office. This activity can only be completed online at http://gplearning.racgp.org.au

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

FOR A FULL LIST OF ABBREVIATIONS AND ACRONYMS USED IN THESE QUESTIONS PLEASE GO TO PAGE 3.
FOR EACH QUESTION BELOW SELECT ONE OPTION ONLY.

QUESTION 1

You have been notified that Jackson, a student aged 16 years, died suddenly over the weekend while playing football for his local team. Jackson's family has been seeing you for more than 20 years and Jackson has been your patient for the whole of his life. Jackson was not taking any medications and had no significant medical history. You do not recall any family history of cardiovascular disease. Which of the following statements is NOT true?

A. The causes of sudden cardiac death in young people like Jackson are inherited and are mainly due to rare autosomal recessive conditions.

B. The causes of sudden cardiac death can be categorised as being underpinned by structural diseases of the heart or non-structural diseases.

C. Hypertrophic cardiomyopathy is one of the most common findings at autopsy in young people following sudden cardiac death.

D. First-degree relatives of people dying from sudden death have a 50% chance of carrying a gene mutation and should be referred to a cardiologist for clinical evaluation.

E. Underlying or undiagnosed cardiomyopathy, myocarditis and/or congenital heart disease may account for Jackson's sudden death.

QUESTION 2

Penelope, aged 49 years, presents complaining of calf muscle tenderness and pain of several days duration. She was recently started on hormone replacement therapy (HRT) to manage hot flushes and night sweats, and takes no other medications. There is no family history of thrombophilia. Examination of her calf reveals an area of skin with significant signs of inflammation, including redness, swelling and heat. There are no varicose veins. Which of the following statements is NOT true?

A. Calf vein thrombosis should not be ignored as it carries a degree of risk for pulmonary embolism.

B. Penelope's use of HRT may have precipitated her current problem.

C. Either an antiplatelet agent like aspirin or an anticoagulant such as warfarin could be used to manage Penelope's problem; in the absence of varicose veins she would not benefit from wearing compression stockings.

D. Superficial venous thrombus has a risk of extension of the thrombus, to involve the deep vein system.

E. As Penelope does not have varicose veins, superficial thrombophlebitis can be ruled out.

QUESTION 3

Non-pharmacological management of patients with heart failure is an important part of the overall management plan. All patients should be provided with information about non-pharmacological management strategies that may be of benefit to them. Which of the following statements regarding the non-pharmacological management of patients with heart failure is NOT true?

A. People with heart failure should be provided with information to help them monitor and manage their fluid balance.

B. People with heart failure should be encouraged to weigh themselves before breakfast on a daily basis.

C. Exercise is recommended in those with stable heart failure as this may improve symptoms and functional capacity.

D. Vaccination against influenza and pneumococcal disease should be recommended to all patients.

E. Restriction of both sodium (<2 g/day) and fluid intake (<1.5 L/day) is routinely recommended for all people with heart failure.

QUESTION 4

David, aged 79 years, is a retired soldier who presents complaining of recent tiredness, dizziness and a funny fluttering feeling in his heart, even at rest. He takes a low dose thiazide and an ACEI for his hypertension, and artovostatin for his dyslipidaemia. Occasionally, he uses paracetamol to manage joint pain. Examination reveals a blood pressure of blood pressure of 134/76 mmHg and an irregular heart rate of 136 bpm. Which of the following is the NOT correct?

A. David may have atrial fibrillation (AF) and should be referred for standard investigations, including a 12-lead ECG and an echocardiogram.

B. If David was diagnosed with AF, his CHADS2 score would be 2 and he would be classified as having a high risk of stroke (4% per 100 years without treatment).

C. If David was diagnosed with AF and he developed renal impairment while using an anticoagulant agent, the dose of his anticoagulant agent would need to be reduced.

D. In contrast to warfarin, the newer anticoagulant agents require no routine monitoring.

E. If David has AF confirmed and he had a previous history of TIA, his CHADS2 score would be 4 and he would be classified as having a high risk of stroke (8.5% per 100 years without treatment).

QUESTION 5

In primary prevention of CVD, assessment of an individual's cardiovascular risk on the basis of consideration of multiple risk factors (absolute risk) is more accurate than use of a single risk factor (e.g. cholesterol, blood pressure) for determining risk and for making treatment decisions. Absolute cardiovascular disease guidelines recommend calculating the numerical probability of an event for each patient using the Australian cardiovascular risk charts. Which of the following statements is NOT correct?

A. Lifestyle recommendations to reduce cardiovascular risk should be offered to all patients regardless of their calculated level of risk.

B. The person's calculated level of risk will determine whether they require pharmacotherapy or not.

C. For those calculated to have a low or moderate cardiovascular risk, medication is not routinely recommended.

D. People in primary prevention settings known to have a high baseline risk of cardiovascular disease do not need to have their risk calculated, as they can be assumed to be at high risk.

E. In primary prevention, low dose aspirin is routinely recommended for those at high risk of cardiovascular disease.

QUESTION 6

Christine, aged 20 years, was an only child and an Olympic athlete who died suddenly while training interstate. Her body has been flown back to your hometown for post-mortem examination. Her distraught parents have made an appointment to talk to you. Her mother is extremely distressed as she lost her younger brother suddenly under similar circumstances 50 years ago. Which of the following statements is NOT correct?

A. A family history of sudden death, albeit 50 years ago, is suggestive of a familial propensity for sudden cardiac death.

B. Guidelines for autopsies performed on people who have died suddenly at a young age, like Christine, recommend a toxicology screen, exclusion of non-cardiac causses of death, examination of the heart and under certain circumstances collection of tissue or blood for DNA extraction.

C. If no cause of death is found at autopsy, members of Christine's family do not need to be referred for clinical assessment or genetic investigation.

D. Christine's family might benefit from referral to resources and services available to help families where there has been a sudden cardiac death in the family.

E. Christine's parents and siblings should be referred to, and encouraged to attend, a cardiologist for initial and possibly ongoing clinical screening.

QUESTION 7

Marla, aged 68 years, is a recently retired music teacher. She arrived at your clinic before opening hours and without an appointment, asking to urgently see you. She looks distressed and complains of sudden-onset shortness of breath and sharp chest pain, which feels worse when taking deep breaths. She feels anxious and light-headed. Her symptoms commenced around midnight last night, as she was preparing for bed. She also reports that she did not sleep well last night. Significant medical history includes recent knee surgery and invasive breast cancer diagnosed 5 months ago, for which she is still being treated. Which of the following statements is/are correct?

A. Marla should be reviewed immediately, as her signs and symptoms are consistent with possible pulmonary embolism (PE) or another more serious problem.

B. Marla's medical history, particularly her history of cancer and recent knee surgery, confers an increased risk for deep vein thrombosis (DVT) and/or PE.

C. Warfarin or rivaroxaban would be appropriate anticoagulants to prescribe for Marla if she was diagnosed with PE.

D. All of the above are correct.

E. All of the above are incorrect.

QUESTION 8

Josie is 73 years old and is an active retiree but recently diagnosed with Class II heart failure. Significant medical history includes hypertension, diagnosed 16 years ago, and dyslipidaemia, diagnosed 11 years ago. She had a basal cell carcinoma removed recently from her forearm. Which of the following statements is NOT correct?

A. If Josie was being treated with a beta-blocker (e.g. atenolol) for her hypertension at the time of diagnosis of her heart failure, that treatment should have been stopped and an ACEI commenced immediately.

B. If Josie was being treating with ramipril for her hypertension at the time of diagnosis of her heart failure, that treatment should have been stopped and a heart-failure-specific ACEI commenced at maximal total daily doses, immediately.

C. ACEIs (or angiotensin receptor blockers in patients intolerant of ACEIs), heart failure beta-blockers and mineralocorticoid receptor antagonists prolong survival in patients with symptomatic systolic heart failure.

D. If Josie was being treated with a mid-level dose of ramipril for her hypertension at the time of diagnosis of her heart failure,

she should have the dose slowly titrated to the highest tolerable maintenance dose or dose recommended for use in heart failure.

E. If Josie was being treating with the highest dose of ramipril for her hypertension at the time of diagnosis of her heart failure, she should continue being treated on that dose.

QUESTION 9

With the recent registration and PBS listing of a number of new oral anticoagulant agents, patients diagnosed with non-valvular AF have a range of options to choose from, including warfarin, dabigatran, rivaroxaban and apixaban, depending on whether they meet current PBS criteria for the newer agents. Which of the following statements is NOT correct regarding the currently available oral anticoagulant agents?

A. Patients need to meet strict PBS criteria to qualify for an authority script for all new oral anticoagulant agents.

B. A defining feature of the new oral anticoagulant agents is the lack of antidote to manage over-coagulation and/or uncontrollable bleeding

C. The new oral anticoagulant agents have a different mechanism of action, compared with warfarin.

D. The new oral anticoagulant agents can be monitored to manage over- and undercoagulation.

E. Use of an oral anticoagulant agent may need to be ceased before surgery, depending on the type of surgery/procedure and the associated risk of bleeding.

QUESTION 10

Andrea, a sales assistant aged 46 years, presents to discuss the results of her recent health assessment for people aged 45–49 years. You previously explained the need to collect baseline data to assess her absolute risk of CVD. Andrea has a strong family history of CVD (her father had a non-fatal heart attack at the age of 59 years; her grandfather had a fatal heart attack at the age of 63 years). She smokes but is trying to cut down (currently she smokes half a pack but had previously smoked one pack/day) and she is overweight (BMI is 31.2 m^2/kg). Using the results of her recent lipid profile and today's BP result, her absolute risk of cardiovascular risk is calculated to be 15% using an online calculator. Which of the answers below is CORRECT in terms of describing the implications of her calculated cardiovascular risk?

A. Andrea should be provided with lifestyle information especially about diet and exercise, and smoking cessation.

B. Andrea is at a very high risk of a cardiovascular event over the next 5 years and should be treated aggressively with lipid-lowering therapy, a BP-lowering medication and low dose aspirin.

C. She is at a high risk of a cardiovascular event over the next 5 years and should be treated aggressively with lipid-lowering therapy, a BP-lowering medication but not low dose aspirin.

D. She is at moderate risk of a cardiovascular event over the next 5 years and pharmacotherapy is routinely recommended by current guidelines.

E. Her calculated risk is a true reflection of her cardiovascular risk and is neither an overestimate nor underestimate of risk.

NOTES

NOTES

check

Independent learning program for GPs

Unit 504 April 2014

Infections

RACGP

www.racgp.org.au/check

Subscriptions

For subscriptions and enquiries please call 1800 331 626 or email check@racgp.org.au

Published by

The Royal Australian College of General Practitioners
100 Wellington Parade
East Melbourne, Victoria 3002, Australia
Telephone 03 8699 0414
Facsimile 03 8699 0400
www.racgp.org.au

ABN 34 000 223 807
ISSN 0812-9630

check

Independent learning program for GPs

Infections

Unit 504 April 2014

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

Many illnesses arise from infection by pathogens, such as bacteria or viruses, causing a wide range of signs and symptoms, which may require very specific and targeted therapies and management.

Bacterial infections can be treated with antibiotics, but these agents provide no benefit for viral infections. Education programs in recent years have focused on reducing inappropriate antibiotic prescribing and creating an awareness of antibiotic resistance.[1]

Immunisation is an important public health initiative for prevention of bacterial and viral infections. In Australia vaccination programs are in place for various target groups and in 2009, for example, 75% of Australians aged 65 years and older were vaccinated against seasonal influenza.[2]

Surveillance and notification of infections, as well as contact tracing, are important public health initiatives, allowing for better health planning and responses to critical situations (eg pandemics).

This unit of *check* will consider a range of common infections of relevance to general practice. The unit will also consider important issues such as antimicrobial resistance, immunisation and notification of reportable diseases.

LEARNING OUTCOMES

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

- summarise the GP's roles and responsibilities in the identification and management of patients with tuberculosis
- explain current guideline management options for asymptomatic bacteriuria
- list initial tests and possible follow-up tests for those suspected of being infected with hepatitis B
- outline key considerations in the management of people with community acquired pneumonia
- identify signs and symptoms that may be suggestive of a urinary tract infection in babies/children of different ages and the elderly
- describe the importance of contact tracing for sexually transmissible infections and ways that contact tracing can be undertaken.

AUTHORS

Nicole Allard MBBS, MPH, FRACGP is a general practitioner at the Joslin Clinic Western Region Health Centre in West Footscray, Melbourne. She works in refugee health and has a special clinical interest in hepatitis B. She is a member of the Viral Hepatitis Special Interest Group of the Australasian Society for Infectious Diseases and The Hepatitis B Working Group for the Department of Health in Victoria. She is currently enrolled as a PhD candidate at the University of Melbourne.

Kym Collins BMed (Hons), FRACGP, FAChSHM is currently senior chief medical officer in HIV and sexual health at Gosford Hospital, sexual assault forensic visiting medical officer (VMO) at Gosford Hospital, and VMO in HIV and sexual health at Albury and Wagga Wagga Base Hospitals. She is interested in education and enhancing the capacity of healthcare workers to talk comfortably about sexual health. She is a member of the GP working group in STIPU and the AChSHM education committee.

Benjamin Cowie, MBBS, PhD, FRACP is an infectious diseases physician with the Victorian Infectious Diseases Service at the Royal Melbourne Hospital, and an epidemiologist at the Victorian Infectious Diseases Reference Laboratory. He is vice president of the Australasian Society for HIV Medicine, and is a member of the Hepatitis B Expert Resource Panel of the Western Pacific Regional Office of the World Health Organization. He is also an honorary senior lecturer in the Department of Medicine at The University of Melbourne.

Justin Denholm, MPH&TM, MBioethics, PhD, FRACP is an infectious diseases physician at the Royal Melbourne and Melbourne Private Hospitals. He has a special interest in tuberculosis, particularly in relation to the diagnosis and management of latent tuberculosis infection.

Miriam Grotowski BMed (Newc), FRACGP, Diploma Psychiatry (ED) is a general practitioner and visiting medical officer at the Hunter New England Area Health Service, a partner at the Smith Street practice in Tamworth and works at a sexual health clinic in Tamworth.

Sara Whitburn BMBS, FRACGP is a general practitioner and family planning doctor working in Melbourne, Victoria, and has a special interest in women's health and children's health, especially early childhood.

May Wong MBBS is a conjoint associate lecturer at the University of New South Wales and currently works at Bankstown Lidcombe Hospital.

PEER REVIEWERS

Gary Franks MBBS, JP is a medical coordinator and general practitioner at the Illawong Christian Medical Centre. He is also a general practitioner consultant for the National Prescribing Service and a member of the Therapeutics Guidelines Antibiotics Expert Group.

Darren Russell MBBS, FRACGP, DipVen, FAChSHM, FRACP (London) is the Director of Sexual Health at Cairns Hospital and holds adjunct appointments at the level of associate professor at the University of Melbourne and James Cook University. He is also the chair of the HIV Foundation, Queensland, and a board member of the Australasian Society for HIV Medicine. His He has interest in men's sexual health, HIV medicine, viral hepatitis, and Indigenous sexual health.

REFERENCES

1. National Prescribing Service. Media briefing on new NPS Medicinewise 'Antibiotic Resistance' campaign. Sydney: NPS, 2012. Available at www.nps.org.au/media-centre/media-releases/repository/media-briefing-on-new-nps-medicinewise-antibiotic-resistance-campaign [Accessed 19 March 2014].
2. Australian Institute of Health and Welfare 2012. Australia's health 2012. Australia's health series no.13. Cat. no. AUS 156. Canberra: AIHW.

GUIDE TO ABBREVIATIONS AND ACRONYMS IN THIS UNIT OF *CHECK*

ACAPS	Australian CAP study	ESR	erythrocyte sedimentation rate	NAAT	nucleic acid amplification test
AFB	acid-fast bacilli	FBE	full blood examination	PCR	polymerase chain reaction
ALT	alanine transaminase	ECG	electrocardiogram	RPM	respirations per minute
Anti-HBs	hepatitis B surface antibody	HAV	hepatitis A virus	STI	sexually transmissible infection
Anti-HBc	hepatitis B core antibody	HBsAg	hepatitis B surface antigen	TB	tuberculosis
ASHM	Australian Society of HIV Medicine	HBV	hepatitis B virus	TIA	transient ischaemic attack
BPM	beats per minute	HCC	hepatocellular cancer	UEC	urea, electrolyte and creatinine
CAP	community acquired pneumonia	HCV	hepatits C virus	UTI	urinary tract infection
CHB	chronic hepatitis B	HDV	hepatitis D virus	VUR	vesicoureteral reflux
COPD	chronic obstructive pulmonary disease	HIV	human immunodeficiency virus		
		INR	international normalised ratio		
CRP	C-reactive protein	LFT	liver function test		
CrCl	creatinine clearance	LTBI	latent tuberculosis infection		
EBV	Epstein-Barr virus	MSM	men who have sex with men		

CASE 1

SANJIV HAS A COUGH

Sanjiv, 31 years of age, emigrated from India 18 months ago. You met his wife when she brought their young children, aged 2 and 4 years, for vaccinations last year. Sanjiv tells you that he has had a productive cough for the past 4 weeks and feels tired and run down.

QUESTION 1

What questions will you ask Sanjiv about his cough to help clarify the likely diagnosis?

FURTHER INFORMATION

Sanjiv tells you that he had been well prior to this illness. He lost 2–3 kg over the past month and has had intermittent subjective fevers but has not had any haemoptysis. He smokes 3–4 cigarettes per day and currently takes no medications.

QUESTION 2

What are the most important diagnoses to consider for Sanjiv? What tests will you perform?

FURTHER INFORMATION

Sanjiv is concerned when you discuss tuberculosis (TB) as a possible diagnosis. He says that he was tested for TB when he came to Australia and the test was negative. He asks how he could have contracted TB in Australia.

QUESTION 3

How will you answer Sanjiv?

FURTHER INFORMATION

Sanjiv's test results are shown below.

- Sputum microscopy, culture and sensitivity: leukocytes ++, upper respiratory tract flora
- Sputum Ziehl-Neelson stain: AFB (acid-fast bacilli) seen ++
- Sputum AFB culture: pending

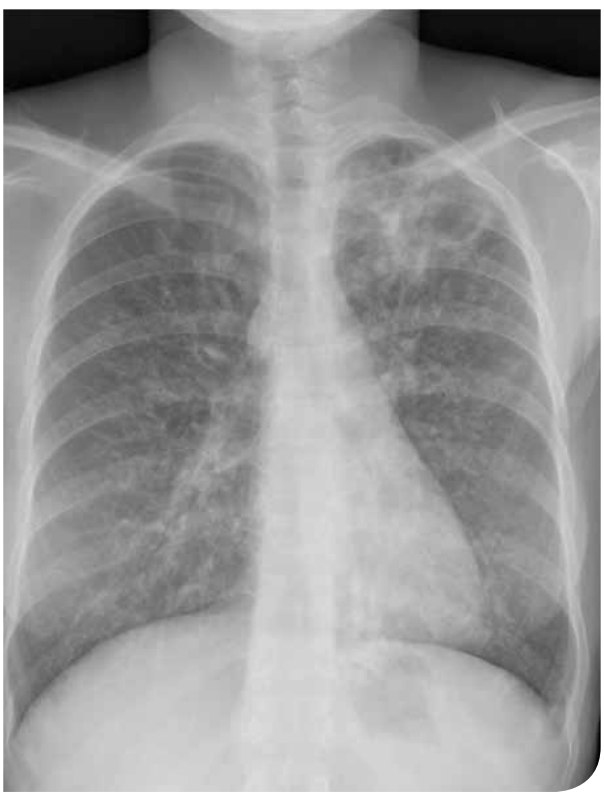

Figure 1. Chest X-ray

QUESTION 4

What do these test results mean? What are your next steps in managing Sanjiv?

FURTHER INFORMATION

Sanjiv is worried about his family's exposure to TB because of his illness. He asks if you can test his family to see if they have been infected, and whether anything can be done to stop them becoming sick.

QUESTION 5

How will you respond? How should his family be managed?

CASE 1 ANSWERS

ANSWER 1

Sanjiv has already mentioned that the cough is productive and has persisted for 4 weeks, which makes common differential diagnoses such as viral respiratory infections (eg acute bronchitis) less likely. Associated features, such as the presence of fever, weight loss or coughing up blood (haemoptysis), may help to further clarify the diagnosis. A past medical history should be taken, including smoking history, current medication use and previous respiratory infections. Exposure to sick contacts, animals and any occupational exposures should also be assessed.

ANSWER 2

Given a history of productive cough of more than 3 weeks and emigration from India, TB is the most important and likely diagnosis to consider. Although uncommon in Australian-born individuals, TB should be considered in high-risk groups, including immigrants from high-prevalence areas (eg Afghanistan, South-East Asian countries, Papua New Guinea, the African continent and the Russian Federation) presenting with TB-related symptoms.[1,2]

The development of TB in a person exposed to it has been described as a two-step process. Rapid progression to TB occurs within 2 years of infection in approximately 5% of people[3] and, overall, 10–15% of infected people will develop active TB at some stage later in life.[4]

Differential diagnosis should include pertussis infection; however, this is less likely to be associated with prolonged sputum production and weight loss. Other causes of prolonged productive cough and weight loss, such as lung cancer, are less likely given his age and ethnicity, but should still be considered in a diagnostic assessment. Symptoms of TB may include a cough of 3 weeks duration or longer, chest pain, haemoptysis or sputum, weakness/fatigue, lack of appetite and weight loss, chills, fever and night sweats.[5] Haemoptysis may be present in TB but is frequently absent and does not exclude the diagnosis.[6] Smoking increases the risk of lung cancer but it also roughly doubles the risk of TB.[7]

In the first instance, Sanjiv should have a chest X-ray. Sputum testing should be ordered for acid-fast bacilli (AFB) microscopy and culture. A new polymerase chain reaction (PCR) test is now also available, which some experts recommend.[8–10] Three early morning sputum samples should be collected on three separate days to maximise sensitivity.[8–10]

Testing for latent tuberculosis infection (LTBI) using, for example, the tuberculin skin test or interferon-gamma release assay, should not be performed in this setting as it may provide false negative results in active disease.[11]

ANSWER 3

In many countries there is a considerable stigma associated with TB and there may be a reluctance to consider this diagnosis. Sanjiv would have had a chest X-ray during his immigration screening process as that is a requirement for most immigrants.[12] The screening program is intended primarily to identify people with evidence of active TB, which Sanjiv apparently did not have when he was screened. However, people exposed to TB before migration may contract LTBI, which is frequently found in people with normal chest X-rays. About 20% of immigrants from the Indian subcontinent have LTBI but many will have no recollection of a specific exposure.[13] LTBI is asymptomatic but may be reactivated many years after migration.[14] Sanjiv, therefore, is much more likely to have contracted LTBI in India rather than a more recent exposure in Australia.

ANSWER 4

Sanjiv's chest X-ray shows left upper lobe pneumonia with cavitation, which is typical for reactivated TB. His sputum smear is positive for AFB, which is consistent with TB. Other AFB could include non-tuberculous mycobacteria or nocardia, both of which are less likely to be the cause of this illness. Sputum cultures for TB can take up to 4–6 weeks to grow, so you should not wait for the results before initiating further management. The new PCR test provides results within a day; however, the validity of these tests is under review by national expert groups.[7]

Guidelines recommend that people with TB should be managed in close consultation with appropriately trained specialists.[1] It would be appropriate at this time to refer Sanjiv to a hospital-based infectious diseases or respiratory service. He should be admitted to hospital for further assessment and isolation, given the risk of TB transmission. He would most likely be started on TB therapy as an inpatient and have further laboratory tests for confirmation of TB, such as TB PCR on sputum. Identification of drug susceptibility will be performed when cultures are positive.[15]

Each state or territory department of health requires notification of the confirmed diagnosis and treatment plan.[1] In Sanjiv's case, the notification would be most appropriately done in hospital after his diagnosis is confirmed.

ANSWER 5

Close household contacts are at risk of contracting TB, and treatment is available to prevent progress to TB disease (most commonly with isoniazid). Children under the age of 5 years are at a much higher risk of rapid progression to active disease, including TB meningitis. Tests for LTBI, including the interferon-gamma release assay and tuberculin skin test, can be performed. Responsibility for conducting such testing lies with the Department of Health, which will undertake a contact tracing exercise after each diagnosis of TB. Sanjiv and his family should be counselled regarding the benefits of screening and encouraged to participate in screening. They should be advised that treatment to prevent TB disease is available for any family member likely to have been infected.[16]

RESOURCES FOR PATIENTS

- Victorian Department of Health. Better Health Channel. Tuberculosis (TB). Available at www.betterhealth.vic.gov.au/bhcv2/bhcarticles.nsf/pages/Tuberculosis_(TB) [Accessed 20 February 2012].
- Victorian Department of Health. Better Health Channel. Tuberculosis treatment. Available at www.betterhealth.vic.gov.au/bhcv2/bhcarticles.nsf/pages/Tuberculosis_treatment [Accessed 20 February 2014].

REFERENCES

1. Respiratory Expert Group. Mycobacterial infections, Pulmonary Tuberculosis, Tuberculosis overview (revised June 2010) In: eTG Complete [Internet] Melbourne. Therapeutic Guidelines Ltd. 2013. Available at tg.org.au [Accessed 28 January 2014].
2. World Health Organization. Tuberculosis, TB data visualization, estimated TB cases and deaths, 1990–2012. Available at www.who.int/tb/country/data/visualizations/en/index.html [Accessed 28 January 2014].
3. Sutherland I. The ten-year incidence of clinical tuberculosis following 'conversion' in 2550 individuals aged 14 to 19 at the time of conversion. TSRU progress report. The Hague: KNCV 1968.
4. Maher D. The natural history of Mycobacterium tuberculosis infection in adults. In: Schaaf HS, Zumla A, editors. Tuberculosis: a comprehensive clinical reference. London: WB Saunders Elsevier Health Sciences, 2009. Chapter 13:129–32.
5. Centres for disease control and prevention. Learn the signs and symptoms of TB disease. Available at www.cdc.gov/features/tbsymptoms/ [Accessed 20 February 2014].
6. Miller LG, Asch SM, Yu EI, Knowles L, Gelberg L, Davidson P.A population-based survey of tuberculosis symptoms: how atypical are atypical presentations? Clin Infect Dis 2000;30:293–99.
7. Lin HH, Ezzati M, Murray M. Tobacco smoke, indoor air pollution and tuberculosis: a systematic review and meta-analysis. PLoS Med 2007;4:e20. doi:10.1371/journal.pmed.0040020.
8. Communicable Diseases Network Australia: National guidelines for the public health management of TB. Available at www.health.gov.au/internet/main/publishing.nsf/Content/D140EDF48C0A0CEACA257BF0001A3537/$File/TB-SoNG-July-2013.pdf [Accessed 28 January 2014].
9. Coulter C. Tuberculosis testing. Aust Fam Physician 2012:41:489–92.
10. National Institute for Health Care and Excellence. Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control. NICE Clinical Guidelines 117. Available at www.guidance.nice.org.uk/cg117 [Accessed 28 January 2014].
11. Kobashi Y, Mouri K, Yagi S, et al Clinical utility of the quantiferon TB-2g test for elderly patients with active tuberculosis. Chest 2008;133:1196–02.
12. Flynn M, Brown L, Tesfai A, Lauer T. Post-migration screening for active tuberculosis in Victoria, Australia. Int J Tuberculosis Lung Dis 2012;16:50–55.
13. Pareek M, Watson JP, Ormerod LP, et al. Screening of immigrants in the UK for imported latent tuberculosis: a multicentre cohort study and cost-effectiveness analysis. Lancet Infect Dis 2011;11:435–44.
14. McBryde ES, Denholm JT. Risk of active tuberculosis in immigrants: effects of age, region of origin and time since arrival in a low-exposure setting. Med J Aust 2012; 197:458–61.
15. McBryde ES, Denholm JT, Eisen DP, Street AS. Management of tuberculosis. Parkville: Victorian Infectious Diseases Service; 2012. Available at www.vids.org.au/ckfinder/userfiles/files/VIDSTBMx_WebVersion(1).pdf [Accessed 25 February 2014].
16. Denholm, JT, Street, AC. Diagnosis and management of latent tuberculosis infection. Med Today 2010;11:72–76.

CASE 2

FLORENCE IS VERY QUIET AND WITHDRAWN

Florence is 88 years of age and you see her regularly when visiting the local nursing home. She is very quiet, forgetful and withdrawn. The staff tell you that she has been like this for the past 48 hours. Last night she was very agitated and was unable to sleep. Florence has a past history of a transient ischaemic attacks (TIAs), mild cognitive decline, renal dysfunction, hypertension and occasional urinary incontinence.

QUESTION 1

What could be causing Florence's behavioural change? How would you assess her?

FURTHER INFORMATION

Florence does not recognise you and doesn't want to talk. However, she doesn't object to your examination. She has a temperature of 37.5°C. Her ears, throat and chest are clear but she has some mild lower abdominal discomfort. You ask the staff to collect a urine sample as part of her organic screen, which they obtain later that day. A dipstick is positive for leucocytes, nitrates and blood, and a culture grows *Escherichia coli,* 10^8 units/mL.

QUESTION 2

What is the diagnosis?

QUESTION 3

How would you treat Florence?

FURTHER INFORMATION

Florence's fever, abdominal symptoms and delirium improve but a few months later she is unwell again with pneumonia that requires hospital admission. Her incontinence worsens and she is discharged with an indwelling catheter for administration of antibiotics at the nursing home. The staff notice that her urine in the bag is cloudy and do a dipstick test, which shows leucocytes and nitrates; however, Florence feels well.

QUESTION 4

What could be causing leucocytes and nitrates to appear in her urine?

QUESTION 5

What criteria might you use to determine if Florence needs treatment?

CASE 2 ANSWERS

ANSWER 1

Florence is showing signs of delirium (withdrawal, insomnia and restlessness). Delirium is characterised by a rapid onset of cognitive and behavioural changes, and fluctuating symptoms. It may have a short duration (days–weeks); however, symptoms may persist for several months.[1] Delirium can have various multiple causes, such as infection, metabolic disorders, pain, dehydration, drug effects, urinary retention or cancer.

Assessment should include a through history of the recent behavioural changes, medication review, organic screen of urea, electrolyte and creatinine (UEC), full blood examination (FBE), erythrocyte sedimentation rate (ESR), vitamin B12, folate, urinalysis and chest X-ray.[1] Additional tests or investigation (eg ECG) may be considered depending on the results of the initial assessment.

ANSWER 2

Florence has a urinary tract infection (UTI), which is the most likely cause of her delirium. Diagnosis of bacterial UTIs is made on the basis of presenting symptoms and is confirmed by the presence of significant uropathogenic bacteria in the urine.[2]

UTIs are common in the elderly. The incidence increases with age and is more prevalent in elderly people in residential care than those still living at home.[3] UTIs in the elderly can be complicated as they often occur on a background of functional and structural abnormalities of the genitourinary system as well as comorbidities. Compared with younger patients, UTIs in the elderly often have more serious consequences, such as delirium, dehydration, urosepsis, hospitalisation or even death.[3]

ANSWER 3

The recommended oral antibiotic regimen for adult non-pregnant women include:

- trimethoprim 300 mg daily for 3 days
- cephalexin 500 mg 12-hourly for 5 days
- amoxicillin and clavulanate 500+125 mg 12-hourly for 5 days.

Another option is nitrofurantoin 100 mg 12-hourly for 5 days but it should not be used in those with renal impairment because of the inability to achieve necessary concentrations in the urine and the possibility of toxic levels in the plasma.[4]

Note that urine alkalinising agents will not interfere with the efficacy of antimicrobial medication and may help relieve the discomfort associated with UTI symptoms. The exception is use of nitrofurantoin with alkalinising agents, where the rate of nitrofurantoin excretion may be increased.[2] Alkalinising agents should not be used for those with a creatinine clearance (CrCl) of <30 mL/minute.[5]

Guidelines support recommending that patients have a high fluid intake and complete bladder emptying to assist antimicrobial therapy.[4]

Elderly patients are at a higher risk of drug interactions and adverse effects. A 2008 Cochrane review of studies investigating antibiotics in older women reviewed 15 studies comparing short and longer-term antibiotics.[6] It found that short-course treatment (3–6 days) was sufficient for treating uncomplicated UTIs in elderly women and had fewer adverse effects, but concluded more studies were needed in the older age group and in the community.[6]

ANSWER 4

As Florence is well and has no pain or change in mental state, the most likely cause is asymptomatic bacteriuria, which is very common in the elderly population. Studies have found a prevalence of asymptomatic bacteriuria of 15–50% among people in residential care.[7] The prevalence is more common with the use of urinary catheters and external urine collection, as well as in patients with cognitive impairment and urinary and faecal incontinence.[7]

Catheterisation allows for the formation of a biofilm between the catheter and urethral mucosa.[8] A biofilm is the aggregation of microorganisms that form a structure on solid surfaces. The greatest risk factor for catheter-associated UTI is duration of catheterisation.[9]

ANSWER 5

Current guidelines do not recommended screening for asymptomatic bacteriuria in the elderly;[2,10] however, there are times when patients may have physical, mental or behavioural changes and a screen for infection may be required.

Asymptomatic bacteriuria should not be treated with antimicrobial therapy, as treatment has been implicated in the emergence of more resistant organisms. Criteria have been recommended to help establish if there is a need for initiating antibiotics in older patients in long-term care with indwelling catheters. These criteria include the presence of fever >37.9°C or 1.5°C above baseline temperature, new abdominal or pelvic tenderness, rigors without obvious cause, or new onset of delirium.[5,11] Samples for culture should always be taken through a newly inserted catheter.[12]

Catheters should be replaced before commencing antibiotic therapy in symptomatic catheterised patients if a catheter has been in situ for more than 1 week. Catheters that have been in use for more than 2 weeks should be changed to try to achieve a quicker resolution of symptoms and to prevent UTI recurrence.[8] The optimal method of decreasing catheter-associated UTIs is to reduce indwelling catheter use and remove catheters as soon as they are no longer clinically necessary.[12]

Current Australian guidelines do not support routine use of prophylactic antibiotics at the time of catheter placement, change or removal.[12]

REFERENCES

1. Commonwealth of Australia Department of Health. Delirium in Older People booklet. Available at www.health.gov.au/internet/main/publishing.nsf/Content/4F8338AEFA71A16ECA257BF0001F4054/$File/DeliriuminOlderPeople.pdf [Accessed 20 February 2014].

2. Antibiotic Expert Group. Antibiotics: Introduction. In: eTG [Internet]. Melbourne: Therapeutic Guidelines Ltd; 2012. Available at www.tg.org.au [Accessed 20 February 2014].
3. Calijouw MAA, den Elzen WPJ, Cools HJM, Gussekloo J. Predictive factors of urinary tract infections among the oldest old in the general population. A population-based prospective follow-up study. BMC Medicine 2011;9:57. Available at www.biomedcentral.com/1741-7015/9/57 [Accessed 24 January 2014].
4. Antibiotic Expert Group. Therapeutic guidelines: antibiotics: urinary tract infections: acute cystitis. In: eTG [Internet]. Melbourne: Therapeutic Guidelines Ltd; 2012. Available at www.tg.org.au [Accessed 20 February 2014].
5. Rossi S, editor. Urinary alkalinisers and acidifiers. Australian Medicines Handbook. In: Australian Medicines Handbook 2014. Adelaide: Australian Medicines Handbook Pty Ltd; 2014. Available at www. amh.net.au [Accessed 3 February 2014].
6. Lutters M, Vogt-Ferrier NB. Antibiotic duration for treating uncomplicated, symptomatic lower urinary tract infections in elderly women. Cochrane Database Syst Rev 2008;16:CD001535. Available at http://onlinelibrary.wiley.com/store/10.1002/14651858.CD001535.pub2/asset/CD001535.pdf;jsessionid=5F080C38CAC39B40CA9C70C280A3AC33.f04t02?v=1&t=hrvm1o09&s=57e2191bb17438b583ff68d0cdda5021396df530 [Accessed 20 February 2014].
7. Nicolle LE and Yoshikawa TT. Urinary tract infection in long-term-care facility residents. Clin Infect Dis 2000;31:757–61.
8. Hooton TM, Bradley SF, Cardenas DD, et al. Infectious Diseases Society of America. Diagnosis prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. Clin Infect Dis 2010;50:625–63.
9. Stamm WE, Raz P. Factors contributing to susceptibility of postmenopausal women to recurrent urinary tract infections. Clin Infect Dis 1999;28:723–25.
10. Jarvis TR, Chan, L, Gottlieb, T. Assessment and management of lower urinary tract infections in adults. Aust Prescrib 2014:37:7–9.
11. Loeb M, Bentley DW, Bradley S, et al. Development of minimum criteria for the initiation of antibiotics in residents of long-term-care facilities: results of a consensus conference. Infect Control Hosp Epidemiol 2001;22:120–24.
12. Therapeutic guidelines: Antibiotics: urinary tract infections: catheter-associated bacteruiria and urinary tract inections. In: eTG [Internet]. Melbourne: Therapeutic Guidelines Ltd; 2012. Available at www.tg.org.au [Accessed 20 February 2014].

CASE 3

MICHAEL HAS A NEW PARTNER

Michael, a Nigerian aged 24 years, arrived in Australia 3 years ago on a student visa. He has been experiencing tiredness, loss of appetite and a general sense of feeling run down. He is fluent in English and does not require an interpreter when he sees you.

After history taking and examination, you discover that he has a new female partner and that neither Michael nor his partner has ever been screened for viral infections. Following appropriate counselling, you offer testing for bloodborne viral infections and sexually transmissible infections (STIs) as part of the health screening. You obtain his consent for testing. He has no significant history or family history.

QUESTION 1

What tests would you order?

FURTHER INFORMATION

Michael returns to your practice 2 weeks later for his results. The results of Michael's hepatitis B serology are:

- HBsAg positive
- anti-HBs negative
- anti HBc positive.

His other screening tests are negative.

QUESTION 2

What is your interpretation of his hepatitis B results?

QUESTION 3

What information about his condition will you give Michael?

QUESTION 4

What further tests will you arrange for Michael?

FURTHER INFORMATION

Michael's results are as follows:

- HBV DNA 1600 IU/mL
- HBeAg negative and anti-HBe positive
- ALT 45 IU/L
- OTHER LFTs normal
- Ultrasound and AFP normal
- anti-hepatitis A positive
- anti-hepatitis D positive.

Michael sees you 2 weeks later for his results. He is anxious and upset as his new relationship nearly ended after he disclosed his CHB status. He is concerned about the diagnosis and especially worried after you mentioned he required ongoing screening for liver cancer.

On more detailed physical examination he has no signs of liver disease and is at a healthy weight (BMI 23 m^2/kg).

QUESTION 5

What phase of infection is he in?

QUESTION 6

What is the significance of the positive HAV and HDV serology tests?

QUESTION 7

In light of his abnormal ALT, are there any other tests that would assist with assessing his liver?

CASE 3 ANSWERS

ANSWER 1

Screening on request or opportunistically is important for the detection of STIs. This is particularly so in the case of STIs that are likely to be of public health significance but often present asymptomatically in the early stages of infection or may be largely asymptomatic (eg chlamydia).[1]

Having a sexual health check-up is recommended when changing sexual partners or starting a new relationship, as in Michael's case. Provision of appropriate counselling and obtaining consent from patients is necessary.[1,2]

Appropriate tests to order for Michael as part of an asymptomatic sexual health screen include:[1]

- hepatitis B surface antigen (HBsAg)
- hepatitis B surface antibody (anti-HBs)
- hepatitis B core antibody (anti-HBc)
- human immunodeficiency virus antibody (HIV Ab)
- syphillis serology
- chlamydia and gonorrhoea PCR from urine.

Hepatitis C antibody testing is not usually performed unless risk factors are present. Risk factors for HCV include a history of injecting drug use, incarceration, blood transfusions, tattoos or skin piercing and countries with a high prevalence.[3]

ANSWER 2

Michael's results are consistent with a diagnosis of chronic hepatitis B (CHB).[1]

The prevalence of CHB in Australia is about 1% and has increased in the last decade.[4] A higher prevalence of over 8% is reported for those born in endemic areas overseas. Higher rates are also observed in certain groups within Australia. For example, the estimated prevalence is about 3–4% for Aboriginal and Torres Straight Islander peoples, people who have injected drugs and men who have sex with men (MSM).[4–6]

In Australia 56% of people with CHB are estimated to be undiagnosed.[4] Although CHB is most often asymptomatic, it can lead to serious liver disease (eg cancer or cirrhosis) in 15–20% of people if the disease is not well managed.[7]

Given current Australian treatment patterns, it has been predicted that by 2017 there will be a 2–3-fold increase in liver cancer and death due to CHB.[8]

ANSWER 3

Michael most likely acquired the infection perinatally or in early childhood. The biggest burden of disease for CHB is borne by those infected at birth or as children.[5] Pregnant women with hepatitis B virus (HBV) should be referred to a specialist and considered for treatment to reduce the risk of transmission to the baby.[4]

People living with CHB need lifelong medical follow up; support is available through hepatitis organisations and, in some states, multicultural health organisations. Michael should be given information about preventing transmission of HBV, and educated around the need for lifelong monitoring and possible treatment to prevent advancing liver disease and hepatocellular cancer (HCC).

Michael's new partner should be offered testing and vaccination if susceptible. Vaccination is available free of charge through most state or territory health departments. His family members and household contacts should also consider being tested.[9]

Michael needs further tests to determine the phase of his CHB infection, and screening for HCC or liver cancer.

ANSWER 4

The following additional tests should be arranged for Michael:[9]

- HBV DNA level (also called the HBV DNA viral load)
- hepatitis B e antigen and antibody (HBeAg and anti-HBe)
- full blood examination (FBE)
- liver function tests (LFTs)
- prothrombin time (INR)
- alpha-fetoprotein
- hepatitis D virus (HDV) antibody
- hepatitis A virus (HAV) antibody
- liver ultrasound.

All patients should be tested at diagnosis to determine the phase of infection and to check for evidence of liver inflammation or cirrhosis.[10]

HBV is a cause of HCC and patients who are at greater risk of developing liver cancer should be enrolled in liver cancer surveillance and have 6-monthly ultrasound and tests for alpha-fetoprotein (see *Table 1*). Liver cancer surveillance can be provided by the GP or by the specialist. Lesions that are suspicious for HCC require further imaging (eg quadruple phase CT) and discussion with specialty services such as multidisciplinary hepatoma clinics. Liver cancer surveillance is recommended for all people of African descent over 20 years of age living with CHB.[11]

Table 1. Factors associated with increased rates of cirrhosis and/or HCC[12]

- Older age (longer duration of infection)
- Habitual alcohol consumption
- Co-infection with HCV, HDV or HIV
- Carcinogens such as aflatoxin and tobacco
- Male gender
- Family history of HCC
- History of reversion from anti-HBe to HBeAg
- Presence of cirrhosis
- HBV genotype C
- Core promoter mutation

Routine surveillance for liver cancer in CHB has been shown to improve survival in patients and the evidence also indicates that such surveillance is cost-effective.[13–15]

Everyone with CHB requires regular monitoring, the frequency of which will be determined by the patient's individual circumstances (eg phase of disease, damage present). As a minimum, an annual review that includes LFTs, and HBV DNA viral load should be undertaken.[9] Medicare funds annual HBV DNA testing for people positive for HBsAg.[16] HCC surveillance with liver ultrasound every 6 months is also recommended for those at increased risk.[9] The above tests could be incorporated into a chronic diseases management plan (see Resources for doctors).

ANSWER 5

On the basis of his viral load, Michael is in phase 3 (see Natural history of CHB infection[17]for details of CHB phases). However, he does have a raised ALT, which may indicate liver inflammation or damage, either from his HBV infection or another cause.

ANSWER 6

The positive HAV antibody test indicates that he is immune to HAV and does not need to be offered immunisation.[1,10]

A positive antibody test for HDV indicates past or current HDV infection, which increases the risk of HCC. Further testing (HDV RNA PCR) is required to indicate whether Michael has co-infection with the HDV, but the results can be unreliable or difficult to interpret and specialist advice should be obtained.[1,10]

ANSWER 7

Michael should have a further assessment of his liver for evidence of fibrosis or cirrhosis. Transient elastography can be performed in several hospitals and outreach services in Australia; it is now more commonly used than liver biopsy. Evaluation for other causes of liver disease is also necessary.

HDV, sometimes called hepatitis delta, relies on HBV infection to replicate. The prevalence of HDV varies widely between populations but is estimated to affect about 5% of the 218 000[4] people living with HBV infection in Australia.[18] In non-endemic countries such as Australia, HBV/HDV co-infection was previously more commonly associated with injecting drug use although the epidemiology is changing as migration from areas of higher HDV prevalence increases and country of birth becomes an increasingly important determinant.

A positive HDV antibody test should be followed up by HDV RNA PCR testing, which is available at a limited number of laboratories; it is advisable to check for availability and charges.[18]

HBV/HDV co-infection requires specialist management as outcomes are worse than mono-infection and there are special treatment considerations.

RESOURCES FOR PATIENTS

- Hepatitis Australia. Available at www.hepatitisaustralia.com

RESOURCES FOR DOCTORS

- Australasian Society for HIV Medicine. Testing portal: Diagnostic strategies (section 2.2). Further information regarding testing for HBV. testingportal.ashm.org.au
- Australasian Society for HIV Medicine. Decision-making in HBV. Available at http://www.ashm.org.au/images/Publications/DecisionMakingTools/HBV_DecisionMaking_PRINT_May13.pdf
- Victorian Infectious Diseases Reference Laboratory for the Cancer Council. www.hepbhelp.org.au

RESOURCES FOR PATIENTS AND DOCTORS

- Victorian Hepatitis B Alliance information for doctors, community workers, family and friends, and people with hepatitis B. vhba.org.au/
- A plain English educational tool for working with Culturally and Linguistically Diverse communities. www.svhm.org.au/gp/clinics/Pages/Gastroenterology.aspx

REFERENCES

1. Sexual Health Society of Victoria. National Management Guidelines for Sexually Transmissible infections, 2008. Available at www.mshc.org.au/portals/6/nmgfsti.pdf [Accessed on 29 January 2014].
2. Queensland Government: Queensland Health. Conducting sexual health checks, 2012. Available at www.health.qld.gov.au/sexhealth/hp/healthcheck.asp [Accessed 29 January 2014].
3. Australasian Society for HIV Medicine. Testing portal. Available at testingportal.ashm.org.au/hcv/indications-for-hcv-testing [Accessed 12 March 2014].
4. MacLachlan JH, Allard N. The burden of chronic hepatitis B virus infection in Australia, 2011. Aust N Z J Public Health 2013;37:416–22.
5. Australian Government Department of Health and Ageing. National Hepatitis B Strategy 2010–2013. Canberra: Australian Government. 2010. Available at www.health.gov.au/ internet/main/publishing.nsf/Content/ohp-national-strategies-2010-hepb [Accessed 29 January 2014].
6. Preston-Thomas A, Fagan P, Nakata Y. Chronic hepatitis B. Care delivery and patient knowledge in the Torres Strait region of Australia. Aust Fam Physician 2013;42:225–31.
7. Lavanchy D. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. J Viral Hepat 2004;11:97–107.
8. Homewood J, Coory M, Dinh B. Cancer among people living in rural and remote indigenous communities in Queensland; an update 1997–2002. Queensland Health 2005. Available at www.health.qld.gov.au/hic/IIST/info70.pdf [Accessed 25 February 2014].
9. Maclachlan J. Cowie B. Chronic hepatitis B: what's new? Aust Fam Phys 2013;42:448–51.
10. Crawford DHG, Ryan RJ, Phung N. Clinical assessment of patients with hepatitis B virus infection. In: Matthews G, Robotin M, editors. B positive – all you wanted to know about hepatitis B: a guide for primary care providers. Darlinghurst: Australasian Society for HIV Medicine, 2008; Chapter 6, p. 51–56. Available at www.ashm.org.au/images/publications/monographs/b%20positive/b_positive-all_you_wanted_to_know.pdf [Accessed 25 February 2014].
11. Bruix J, Sherman M. Management of hepatocellular carcinoma. Hepatology 2005;42:1208–36.
12. Gastroenterological Society of Australia (GESA). Chronic Hepatitis B Recommendations. Melbourne: Digestive Health Foundation 2009. Available at www.gpv.org.au/files/downloadable_files/Programs/SHED/2009_gdl_HBV%20management%20GESA.pdf [Accessed 18 March 2014].
13. Wong N. et al. Improved survival trend of patients with hepatocellular carcinoma at an Australian tertiary hospital between 1995–2009. Intern Med J 2013;43:197–203.
14. Gane E. Screening for chronic hepatitis B infection in New Zealand: unfinished business. N Z Med J 2005;118:U1344.
15. Robotin MC. et al. Antiviral therapy for hepatitis B-related liver cancer prevention is more cost-effective than cancer screening. J Hepatol 2009;50:990–98.
16. Australian Government Department of Health and Ageing. Medicare Benefits Schedule, May 2013. Australian Government Department of Health and Ageing, 2013. Available at www.mbsonline.gov.au [Accessed 25 February 2014].
17. Gurgis M, Zekry A. Natural history of chronic hepatitis B virus infection. In: Matthews G, Robotin M, editors. All you wanted to know about hepatitis B: a guide for primary care providers. Darlinghurst: Australian Society for HIV Medicine; 2008 Available at www.ashm.org.au/images/publications/monographs/b%20positive/b_positive-all_you_wanted_to_know.pdf [Accessed 31 March 2014].
18. Shadur B, Maclachlan J, Cowie B. Hepatitis D Virus in Victoria 2000–2009. Intern Med J 2013;43:1081–87.

CASE 4

CHRIS BECOMES MORE SHORT OF BREATH

Chris, aged 71 years, comes to see you because he has had a cough and shortness of breath for the past 2 weeks. His cough is productive of purulent sputum. He has also been feeling more tired than usual and has not been able to do any gardening. Mary, Chris' wife, states that he has been having some 'temperatures' and has not been his usual self.

QUESTION 1

What questions would you ask about the history of the presenting complaint and Chris's past medical history?

QUESTION 2

What are some possible causes for Chris's acute respiratory symptoms?

FURTHER INFORMATION

Chris has classic symptoms of community acquired pneumonia (CAP). On further questioning, Chris tells you he has smoked cigarettes (approximately 1 pack per day) since the age of 17 years. His past medical history is significant for COPD and alcohol abuse. He was also treated with azithromycin, a macrolide antibiotic, for sinusitis 8 weeks before his current presentation.

QUESTION 3

Why is his past medical history and recent antibiotic use significant?

FURTHER INFORMATION

On examination, you note that Chris was unwell, sweaty and flushed. He was febrile at 38.5°C, tachycardic at 110 beats per minute (bpm) and tachypnoeic at 28 respirations per minute (rpm). His saturations in room air were 96%. Chest auscultation revealed coarse crepitations on the right side. An impaired percussion note over the affected lobe was elicited.

QUESTION 4

What are some other features of the clinical examination suggestive of CAP? What are some red flags for severe illness?

QUESTION 5

What further investigations would you order?

FURTHER INFORMATION

A chest X-ray showed patchy alveolar shadowing in the right mid and lower zones. Blood tests showed a significant inflammatory response: CRP 337 mg/L raised white cell count and neutrophilia. A diagnosis of CAP was made. His renal function was normal.

QUESTION 6

What are the common organisms responsible for CAP?

QUESTION 7

What treatment and duration of treatment would you recommend for Chris?

FURTHER INFORMATION

Chris's temperature was reduced within 3 days of therapy. However, 3 weeks later, he returns as he continues to have a cough and experiences fatigue.

QUESTION 8

How would you approach this situation?

QUESTION 9

How can a recurrence of CAP be prevented**?**

CASE 4 ANSWERS

ANSWER 1

Important questions to ask regarding the history of the presenting complaint include:

- Was the onset sudden or gradual?
- How long have symptoms been present (days, weeks or months)?
- What is the course of symptoms (have they been worsening or slowly resolving)?
- Is there any haemoptysis?
- Is there any pleuritic chest pain?
- Are there other symptoms such as weight loss, malaise or night sweats, which could suggest an alternative diagnosis such as tuberculosis or malignancy?

You should elicit the following information about Chris's past medical history:

- existing medical conditions or comorbidities such as asthma or chronic obstructive pulmonary disease (COPD) that may worsen outcome(s)
- history of heart failure
- history of immunosuppression
- smoking status (particularly if Chris has a hoarse voice or, in particular, any haemoptysis)
- whether he has an elevated risk of thromboembolic disease.

ANSWER 2

Table 1 outlines possible causes for Chris's acute respiratory symptoms, all of which should be considered in a differential diagnosis.

Table 1: Causes of acute respiratory symptoms

Common causes
• Viral upper respiratory tract infection • Acute bronchitis • CAP • Exacerbation of airways diseases (eg asthma, COPD and bronchiectasis) • Non-respiratory conditions (especially heart failure)
Rarer but important causes
• Non-infectious respiratory conditions (eg neoplasm, pulmonary embolus, interstitial lung disease, hypersensitivity pneumonitis, sarcoidosis) • Other pneumonias (eg tuberculosis, eosinophilic, aspiration, nosocomial, immunosuppressed) • Right middle lobe syndrome • Churg-Strauss syndrome

A patient presenting with cough (either productive or non-productive), pleuritic chest pain, shortness of breath, temperature >38°C and crackles on auscultation shows classic signs and symptoms of community acquired pneumonia (CAP).[1,2] CAP is a potentially serious illness and may be associated with considerable mortality and morbidity, especially in elderly patients and/or those with major comorbidities.[3]

ANSWER 3

CAP refers to pneumonia occurring in community-dwelling people. That is, people who have not been in hospital or have been in hospital less than 48 hours.[4]

The classical presentation of CAP in clinical practice is often altered by the use of antibiotics, pre-existing lower respiratory tract disease, such as COPD and bronchiectasis, and the age of the patient.[5]

The classic symptoms of pneumonia are often absent in the elderly.[6] Non-specific symptoms, such as headache, diarrhoea, loss of mental clarity, somnolence or frank confusion, are also found commonly in elderly patients with pneumonia.[1,2] Fever is less common in older patients compared to younger patients.[2] These symptoms may be a manifestation of the pneumonia itself or of deterioration of pre-existing renal impairment or congestive cardiac failure.[7] It is important to be aware that as confusion may be the only presenting symptom in elderly patients with CAP, this can lead to delayed administration of antibiotics.[8]

ANSWER 4

Table 2 summarises examination findings for CAP and red flags for severe illness. The presence of red flags indicates severe CAP, which requires hospital admission for specialist care.[1]

Table 2. Examination findings in CAP and red flags for severe illness

Examination findings in CAP[9]
• Increased work of breathing such as use of accessory muscles of respiration • Decreased lung expansion • Dull percussion note • Bronchial breath sounds • Increased vocal resonance • Localised crepitations
Red flags for severe illness on clinical examination[1]
• Respiratory rate >30/min, • Systolic blood pressure <90 mmHg, • SaO_2 <92% • Acute confusion • Multi-lobar involvement on chest X-ray • pH <7.35

In older adults, an assessment for the presence of delirium is also required.[10] This can often be suspected through initial history taking and can be supported by a reduced mini mental state examination. Although not reliable in differentiating cognitive impairment from delirium, a score of less than 25 is associated with poorer outcome in CAP.[1]

ANSWER 5

A chest X-ray is required for an accurate diagnosis; the presence of a new infiltrate is considered the gold standard when clinical features are supportive.[1–3] The site of the pneumonia with relevance to the cardiac and mediastinal borders can be identified by the silhouette sign – an intra thoracic lesion touching the heart border or diaphragm will obliterate that border on the chest X-ray. A lesion not anatomically contiguous will not obliterate that border. Additionally, specific findings such as the presence of cavitation should prompt consideration of a specific aetiology. In this case, the presence of tuberculosis, malignancy, aspiration or *Staphylococcus aureus* infection should be considered.[12]

CAP involving more than one lobe and the presence of a pleural effusion may be associated with more severe disease.[13] Up to 40% of CAP can be accompanied by a typically small, uncomplicated parapneumonic effusion[14] but this can progress to a complicated and infected parapneumonic effusion and, eventually, empyema.

Microbiological tests are not usually helpful in diagnosing CAP as they typically offer a low yield.[4] Since empirical antibiotics work well, identifying a pathogen is not helpful nor does it exclude the presence of atypical pathogen.[15] However, failure of the sputum purulence to clear and a requirement for repeated courses of antibiotics should prompt a sputum sample being sent for culture. This is particularly important in patients with chronic respiratory disease as colonisation with organisms such as *Pseudomonas* that do not respond to conventional antibiotics is not uncommon.[16]

Blood tests to consider include:

- leukocytosis (white blood cell count between 15 000/mm^3 and 30 000/mm^3) with a leftward shift
- C-reactive protein (CRP) to monitor progression
- liver function tests as liver function may be deranged in infections with atypical organisms
- electrolytes as an imbalance that may be seen is hyponatraemia, thought to be caused by excess anti-diuretic hormone produced by the diseased lungs.[17]

Other tests to consider include:[1]

- blood culture
- sputum culture for microscopy, culture and sensitivity
- arterial blood gas to assess gas exchange
- serology for mycoplasma, legionella, chlamydia, influenzae and parainfluenzae. A serological diagnosis occurs if there is a 4-fold increase in titre between acute and convalescent phase of illness
- urinary antigen for legionella
- nasal swabs for influenza and nasopharyngeal aspirate.

Obtaining these tests, however, should never delay administration of antimicrobial therapy on an empirical basis because timely administration is critical for a good outcome.[4]

ANSWER 6

The most common bacterial organism associated with CAP is *Streptococcus pneumoniae*, which is responsible for most severe illnesses and death, especially in the elderly. Other bacteria include *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae* and *Legionella* species. *Haemophilus influenzae* is responsible for less than 5% of CAP cases and is seen mainly in people with COPD.[4]

In the prospective Australian CAP Study (ACAPS), a cause for CAP was identified in 46% of patients. The most frequent causative agents were respiratory viruses (15%), *S. pneumoniae* (14%) and *Mycoplasma pneumoniae* (9%).[18]

Typical pneumonia is caused by bacteria such as *S. pneumonia*, which is the most common organism in all settings. Atypical pneumonia is caused by the influenza virus, mycoplasma, chlamydia, legionella, adenovirus or other unidentified microorganism.[1] The patient's age is the main differentiating factor between typical and atypical pneumonia: young adults are more prone to atypical causes and very young and older persons are more predisposed to typical causes.[19] In atypical pneumonia, the chest X-ray abnormalities are often disproportionate to the pulmonary symptoms, and sputum analysis may reveal numerous leukocytes and no organisms.[20]

Some specific groups have a broader range of possible aetiological agents. These include people at risk of aspiration[21] (eg from stroke or Parkinson's disease and drug and alcohol abuse), patients taking immunosuppressive agents (eg for rheumatoid arthritis) or with underlying immune disorders (eg from HIV[22], haematological malignancies and immune deficiencies), recent hospital inpatients, travellers from tropical Australia and overseas. Early specialist advice to consider a broader range of aetiological agents and tailored management is recommended.

ANSWER 7

Therapy regimens are stratified into mild, moderate or severe. Patients with mild CAP can be treated as outpatients, but those with moderate or severe CAP require hospitalisation.[23]

Penicillins remain the cornerstone of CAP management. Gentamicin is added to provide Gram-negative cover for sicker patients in non-tropical areas. In tropical areas, carbapenem is used instead of penicillin.[23]

Most patients with mild CAP can be managed without hospitalisation or use of intravenous antibiotics. Occasionally, patients may be given intravenous benzylpenicillin if they present at an emergency department. Outpatients should receive treatment with antibiotics for 5–7 days, depending on the clinical response. Current Australian guidelines recommend the following:[18]

- amoxycillin 1 g orally, 8-hourly for 5–7 days (in rural and remote areas, where orally administered antibiotics may not be possible, procaine penicillin 1.5 g daily, intramuscular, can be substituted for amoxycillin until significant improvement has occurred; 5 days therapy is usually needed.)

or (if *M. pneumoniae*, *C. pneumoniae* or *Legionella* is suspected)

- doxycycline 200 mg orally, for the first dose, then 100 mg daily for a further 5 days

or

- clarithromycin 250 mg orally, 12-hourly for 5–7 days.[24]

Where there is penicillin hypersensitivity, use doxycycline or clarithromycin. Note that current guidelines report relatively high rates of doxycycline and clarithromycin resistance by some strains of *S. pneumoniae* in some areas.[24]

Guidelines emphasise clinical review of the patient within 24–48 hours.

If no improvement occurs by 48 hours, or a patient review by 48 hours is not possible, dual therapy with amoxycillin plus either doxycycline or clarithromycin could be considered.[24]

If clinical treatment fails, switching to an alternative drug could be considered.[24]

ANSWER 8

Despite an initial good response from antimicrobial therapy with resolution of fever and acute morbidity, it is very common for patients to experience prolonged cough and malaise. Patients should be informed that symptoms might last for a prolonged period.

Worsening of clinical status despite adequate antibiotic therapy should trigger a reassessment of the original clinical impression. First, the diagnosis of infection must be questioned (*Table 3*). Organisms with inherent (eg fungi, mycobacteria, *P. jirovecI*) or acquired (*P. aeruginosa*) resistance to drugs commonly used for pneumonia therapy must also be considered. A secondary infection, such as post-influenza *S. aureus* pneumonia, might prove resistant to initial therapy. Finally, immunodeficiency (eg HIV, haematological malignancy) or anatomical derangement (eg COPD, bronchiectasis, neoplasm) can alter the clinical course of pneumonia and treatment.

A follow-up chest X-ray may be useful to identify complications of pneumonia or a possible new diagnosis given that Chris is a smoker. It should be noted that a chest X-ray may remain abnormal for weeks even in the presence of successful treatment.

Table 3. Complications of pneumonia

- Empyema
- Parapneumonic effusion
- Abscess
- Metastatic infection
- Nosocomial superinfection
- Cavitation

ANSWER 9

Seeking to reduce any risk factors that may increase the chances of developing CAP in patients who have had CAP previously can help to reduce the likelihood of CAP recurrences. Specific preventive measures include:

- encouraging smoking cessation
- administering both pneumococcal and influenza vaccines in a timely manner
- reducing the effect of comorbidities (eg controlling congestive heart failure and hyperglycaemia, managing swallowing disorders)[6]
- providing education about respiratory hygiene[6]

Immunisation against influenza and increasingly resistant pneumococci is important in preventing pneumonia, particularly in immunocompromised and older adults. The RACGP *Guidelines for preventative activities in general practice* recommends that patients aged ≥65 years should receive the annual influenza vaccination in the pre-flu season months.[25] These guidelines also recommend a one-off dose of pneumococcal polysaccharide vaccination (23vPPV) for the prevention of invasive pneumococcal disease in older people, except for those who have a condition that predisposes them to an increased risk of invasive pneumococcal disease.[26] The Centre for Disease Control and Prevention recommends that consideration for vaccination be made for residents of extended-care facilities and patients who have chronic heart and lung disorders, chronic metabolic diseases (including diabetes mellitus), renal dysfunction, haemoglobinopathies or immunosuppression.[27]

REFERENCES

1. Antibiotics Expert Group. Antibiotics, respiratory tract infections: pneumonia, community acquired pneumonia in adults: patient assessment. In: eTG Complete [Internet] Melbourne. Therapeutic Guidelines Ltd. 2013. Available at tg.org.au [Accessed 31 January 2014].
2. Lim WS, Baudouin S, George R, et al. British Thoracic Society guidelines for the management of community acquired pneumonia in adults: update. Thorax 2009;64(Suppl III):iii1–iii55. Available at www.brit thoracic.org.uk/Portals/0/Guidelines/Pneumonia/CAPGuideline-full.pdf [Accessed 21 February 2014].
3. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community acquired pneumonia in adults. Clin Infect Dis 2007; 44 Suppl 2:S27–72.
4. Antibiotics Expert Group. Antibiotics, respiratory tract infections: pneumonia: community acquired pneumonia in adults: introduction. In: eTG Complete [Internet] Melbourne. Therapeutic Guidelines Ltd. 2013. Available at www.tg.org.au [Accessed 31 January 2014].
5. Fernandez-Sabe N, Carratala J, Roson B, et al. Community-acquired pneumonia in very elderly patients: causative organisms, clinical characteristics, and outcomes. Medicine (Baltimore) 2003;82:159–69.
6. Royal Australian College of General Practitioners. Medical care of older persons in residential aged care facilities (silver book). Melbourne: RACGP, 2006. Available at www.racgp.org.au/your-practice/guidelines/silverbook/ [Accessed 25 February 2014].
7. Khand AU, Gemmell I, Rankin AC, Cleland GJF. Clinical events leading to the progression of heart failure: insights from the national database of hospital discharge. Eur Heart J 2001;22:153–64.
8. Waterer GW, Kessler LA, Wunderink RG. Delayed administration of antibiotics and atypical presentation in community acquired pneumonia. Chest 2006;130:11–15.
9. Beovic B, Bonac B, Kese D, et al. Aetiology and clinical presentation of mild community-acquired bacterial pneumonia. Eur J Clin Microbiol Infect Dis 2003;22:584–91.
10. Marrie TJ. Pneumonia in the elderly. Curr Opin Pulm Med 1996;2:192–27.
11. Marrie TJ, Wu L. Factors influencing in-hospital mortality in community-acquired pneumonia: a prospective study of patients not initially admitted to the ICU. Chest 2005;127:1260–1270.
12. Jenkins P. Making Sense of the Chest X-ray: a hands-on guide. 2nd edn New York: CRC Press 2013.
13. Menéndez R, Torres A, Zalacaín R, et al. Risk factors of treatment failure in community acquired pneumonia: implications for disease outcome. Thorax 2004;59:960.
14. Light RW, Girard WM, Jenkinson SG, et al. The incidence and significance

of parapneumonic effusions. Am J Med 1980;69:507–12.

15. Dambrava, PG, Torres, A, Valls, X, et al. Adherence to guidelines' empirical antibiotic recommendations and community-acquired pneumonia outcome. Eur Respir J 2008;32:892–901.
16. Di Pasquale M, Ferrer M, Esperatti M, et al. Assessment of Severity of ICU-Acquired Pneumonia and Association With Etiology. Crit Care Med 2014;42:303.
17. Nair V, Niederman MS, Masani N, Fishbane S. Hyponatremia in community-acquired pneumonia. Am J Nephrol 2007;27:184–90.
18. Charles PG, Whitby M, Fuller AJ, et al. Australian CAP study collaboration. The etiology of community-acquired pneumonia in Australia: why penicillin plus doxycycline or a macrolide is the most appropriate therapy. Clin Infect Dis 2008;46:1513–21.
19. Klapdor B, Ewig S, Pletz MW, et al (CAPNETZ Study Group). Community-acquired pneumonia in younger patients is an entity on its own. Eur Respir J 2012 May;39:1156–61.
20. Schlick W. The problems of treating atypical pneumonia. Antimicrob Chemother 1993;31 Suppl C:111–20.
21. Antibiotics Expert Group. Antibiotics, respiratory tract infections: pneumonia, community acquired pneumonia in adults: aspiration pneumonia. In: eTG Complete [Internet] Melbourne. Therapeutic Guidelines Ltd. 2013. Available at www.tg.org.au [Accessed 31 January 2014].
22. Antibiotics Expert Group. Antibiotics, respiratory tract infections: pneumonia, community acquired pneumonia in adults: pneumonia in the immunocompromised patient. In: eTG Complete [Internet] Melbourne. Therapeutic Guidelines Ltd. 2013. Available at www.g.org.au [Accessed 31 January 2014].
23. Antibiotics, respiratory tract infections: pneumonia, community acquired pneumonia in adults: outpatient treatment. In: eTG Complete [Internet] Melbourne. Therapeutic Guidelines Ltd. 2013. Available at www.tg.org.au [Accessed 31 January 2014].
24. Royal Australian College of General Practitioners Guidelines for preventive activities in general practice, 8th edn. Melbourne: RACGP, 2012.
25. Jefferson T, Di Pietrantonj C, Al-Ansary LA, Ferroni E, Thorning S, Thomas RE. Vaccines for preventing influenza in the elderly. Cochrane Database Syst Rev 2010;7.
26. Moberley S, Holden J, Tatham DP, Andrews RM. Vaccines for preventing pneumococcal infection in adults. Cochrane Database Syst Rev 2008;1.
27. Centres for Disease Control and Prevention. Pneumonia can be prevented – vaccines can help. Centres for Diseases Control and Prevention. Available at www.cdc.gov/features/pneumonia/ [Accessed 3 February 2014].

CASE 5

CHARLIE HAS A FEVER

Charlie is 2 years of age and has had a fever of 39°C for 2 days. His mother brings him to see you. She tells you he is not eating his solids and that his urine has a strong smell to it.

QUESTION 1

How would you approach history taking and examination?

FURTHER INFORMATION

Charlie is alert but appears miserable. He is adequately hydrated. His ears, nose and throat are normal and his chest is clear. He seems a little uncomfortable when you palpate his abdomen. He has no rash.

QUESTION 2

What is the possible diagnosis?

QUESTION 3

Which tests might you perform? What advice would you give his mother?

FURTHER INFORMATION

Charlie's mother manages to obtain a good urine sample and Charlie's urine dipstick shows white cells and nitrates. The sample is sent for culture and shows an *Escherichia coli* growth of 10^8 units/mL. This is Charlie's first UTI.

QUESTION 4

How would you manage Charlie's UTI?

FURTHER INFORMATION

Charlie responds well to the antibiotics; however, he has two more confirmed UTIs over the next 3 months.

QUESTION 5

What would be your management strategy now?

CASE 5 ANSWERS

ANSWER 1

Feverish illness in children is common. However, the cause of fever can be a diagnostic challenge. In most cases the cause is usually viral but fever can also be the presenting feature of a serious bacterial infection. For children presenting with fever, observation of their behaviour and responses is an important aspect of assessment.

History and examination should be targeted to look for red flags associated with serious infections and should include assessment of hydration, ear, nose, throat, chest and abdomen examination, skin colour, presence of skin rashes, activity levels, respiratory rate, heart rate, neck or joint stiffness or other localising signs.[1]

ANSWER 2

With a fever, abdominal discomfort and offensive urine, it is likely that Charlie has a urinary tract infection (UTI) but gastroenteritis or non-specific viral illness are also possible differential diagnoses. Clinical symptoms and signs of a UTI depend on the age of the child (*Table 1*).

Table 1. Signs and symptoms of UTI by age group[1]

Age group	Symptoms and signs		
	< Most common to least common >		
<3 months	Fever Vomiting Lethargy Irritability	Poor feeding Failure to thrive	Abdominal pain Jaundice Haematuria Offensive urine
>3 months pre-verbal	Fever	Abdominal pain Loin tenderness Vomiting Poor feeding	Lethargy Irritability Haematuria Offensive urine Failure to thrive
>3 months verbal	Fever Dysuria	Dysfunctional voiding Incontinence when previously dry Abdominal pain Loin tenderness	Fever Malaise Vomiting Haematuria Offensive urine Cloudy urine

ANSWER 3

Children presenting with an unexplained fever of ≥38°C or symptoms and signs of a UTI should have a urine sample tested within the first 24 hours.[1] Obtaining an uncontaminated sample can prove difficult in younger children. Pads placed in nappies and urine bags have been shown to have high rates of false positives. Catheter and suprapubic aspirate samples have less contamination,[2] but a clean catch technique is non-invasive and useful in the community setting.

A clean catch urine sample is the recommend method for urine collection in children, who are not able to provide a urine sample on request.[1,3] To perform a clean catch, parents should be advised to wash the genitalia with water and then leave the child exposed. Using a sterile urine container they need to catch the mid-part of the urine stream or leave the child exposed with their legs in a frog leg posture and use a dish between their legs to catch the urine flow.[3]

Urinary dipstick tests have poor sensitivity and specificity, and should be used for screening only. Dipstick analysis is most useful at predicting a UTI when both nitrates and leucocyte esterase are positive, but false positives occur frequently so a urine culture is always required if a UTI is suspected.[4] Therapeutic guidelines[5] recommend performing a urine culture in all children presenting with a UTI prior to the administration of antibiotics. Empirical treatment of a UTI is acceptable while awaiting the culture results.[5]

ANSWER 4

Children under 6 months of age with a suspected UTI or any child who is severely unwell should be referred for a paediatric specialist review.[1,3] Children over 12 months who have a mild UTI and are suitable for oral medication can be treated with:

- amoxycillin and clavulanate 22.5+3.2 mg/kg up to 875+125 mg 12-hourly for 5 days or
- cephalexin 12.5 mg/kg (500 mg max) 6-hourly for 5 days or
- trimethoprim 4 mg/kg up to 150 mg, 12-hourly for 5 days or
- (if trimethoprim liquid formulation is not available) trimethoprim and sulphamethoxazole 4+20 mg/kg up to 160+800 mg, 12-hourly for 5 days.[5]

For children, a follow-up culture should be performed at least 48 hours after cessation of antibiotic therapy.[5]

Recent guidelines have suggested a change to the follow-up of first UTIs.[1,6] Previously, it was strongly recommend that children with a UTI have an ultrasound to identify vesicoureteral reflux (VUR). There is now evidence that most children with a first UTI will have a normal ultrasound.[6] It has also been found there is no difference in the treatment effect of prophylactic antibiotics in children with reflux compared with those not using prophylactic antibiotics and so routinely evaluating VUR in children at low risk is no longer recommended.[7]

Children <6 months should have an ultrasound within 6 weeks of contracting a UTI, but for children ≥6 months, a routine ultrasound is no longer recommended during the acute infection stage unless there are signs of an atypical UTI. Atypical UTIs are complicated by septicaemia, poor urine flow, abdominal mass, raised creatinine, failure to respond within 48 hours to a suitable antibiotic or infection with non-*Escherichia coli* organisms. If an ultrasound is abnormal, then paediatric opinion and further imaging are recommended.[1]

ANSWER 5

About 20% of children who have had one UTI experience symptomatic recurrence.[4] Each recurrence should be treated promptly with antibiotics. Antibiotic treatment of each episode is

guided by culture, sensitivities and clinical response. Charlie will also require an ultrasound within 6 weeks of his UTI to investigate the cause of the recurrence, as well as screening for structural abnormalities.[1]

The role of prophylaxis for recurrent UTI in children is unclear. A Cochrane review found that long-term antibiotics seem to reduce the risk of repeated symptomatic UTIs in susceptible children but the benefit is small and must be considered together with the increased risk of microbial resistance.[10] Specialist advice should be sought when contemplating prophylaxis for recurrent UTI in children.[5]

REFERENCES

1. National Institute for Heath and Clinical Excellence. Urinary tract infection in children: diagnosis, treatment and long-term management. Clinical Guideline CG54. London: National Institute for Health and Care Excellence, 2007. Available at guidance.nice.org.uk/CG54 [Accessed 21 February 2014].
2. Finells SM, Caroll AE, Downs SM. Subcommittee on Urinary Tract Infection Technical report – Diagnosis and management of an initial UTI in febrile infants and young children. Pediatrics 2011;128:749–70.
3. Royal Children's Hospital Melbourne. (2011) Urinary tract infection guideline. Available at www.rch.org.au/clinicalguide/guideline_index/Urinary_Tract_Infection_Guideline 2011 [Accessed 24 January 2014].
4. Williams GJ, Hodson EH, Isaacs D, Craig JC. Diagnosis and management of urinary tract infection in children. J Paediatr Child Health 2012;48:296–301.
5. Antibiotics Expert Group. Antibiotics: urinary tract infections in children. In: eTG Complete [Internet] Melbourne. Therapeutic Guidelines Ltd. 2013. Available at www.tg.org.au [Accessed 21 February 2014].
6. American Academy of Paediatrics Subcommittee on Urinary Tract Infection. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. Available at http://pediatrics.aappublications.org/content/early/2011/08/24/peds.2011-1330 [Accessed 27 January 2013].
7. Craig JC, Simpson JM, Williams GJ, et al. Prevention of recurrent urinary tract infection in children with vesi-coureteric reflux and normal renal tracts (PRIVENT) investigators. Antibiotic prophylaxis and recurrent urinary tract infection in children. N Engl J Med 2009;361:1748–59.
8. Williams G, Craig JC. Long-term antibiotics for preventing recurrent urinary tract infection in children. Cochrane Database of Systematic Reviews 2011, Issue 3. Art. No.: CD001534. 2012.

RESOURCES FOR PATIENTS

- Better Health Channel. Urinary tract infections (UTI). Fact sheet currently being reviewed. Available at www.betterhealth.vic.gov.au/bhcv2/bhcarticles.nsf/pages/Urinary_tract_infections [Accessed 3 February 2014].

CASE 6

HEATH'S RASH

Heath, aged 20 years, moved to Sydney last year from a small country town to study engineering. Heath has been sick for the past week and yesterday he developed a rash. He has been at home and comes to see you as you have been the family GP for 20 years. Heath tells you that he started to get a sore throat, fevers and muscle aches about a week ago. Paracetamol helped a little initially, but now he just feels awful. Heath says the rash started yesterday.

You examine Heath and note a fine, pink rash mostly over his torso, sparing his soles and palms. His throat is red, but no exudate is seen. He has tender cervical lymph nodes and also lymph nodes in his axilla and groin. There is no hepatosplenomegaly.

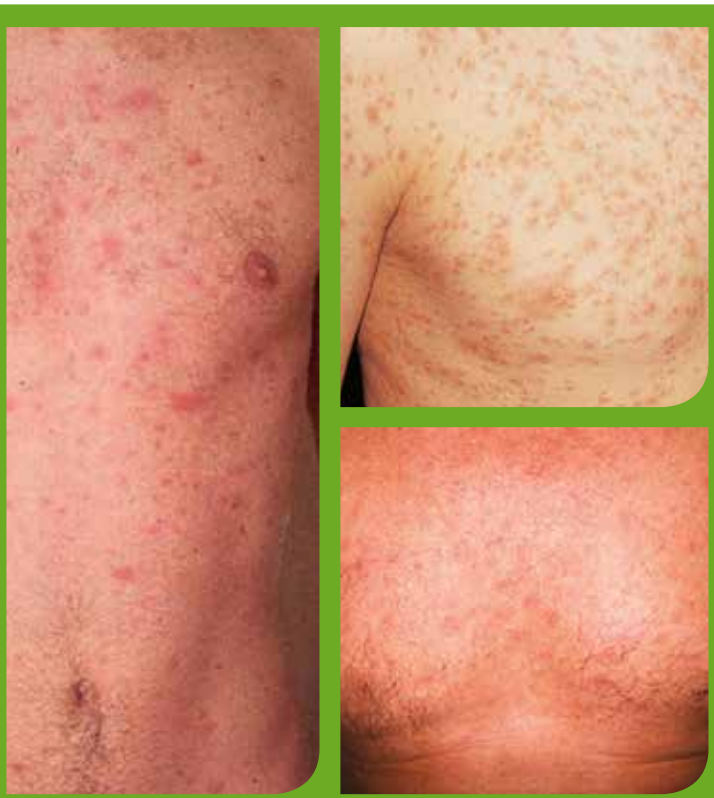

Figure 1a–c: Illustration of HIV seroconversion rash in different individuals

QUESTION 1

What is the differential diagnosis?

QUESTION 2

What tests would you order for Heath?

FURTHER INFORMATION

Heath looks relieved and says that he thinks he is gay, but hasn't told any of his friends or family. He has had some casual male sexual partners whom he met on Grindr and at dance parties. He has oral and anal sex and most of the time he uses condoms. He does not inject drugs but has used some ecstasy. Over the past few months, he has spent a considerable amount of time with one man, Josh, and they have started to have unprotected sex. Their last unprotected anal sexual intercourse was 2 days ago. Heath says that Josh told him he had been 'tested and is clean'. Heath tells you he has never had a sexual health screen.

QUESTION 3

What do you need to discuss with a patient when you order an HIV test?

QUESTION 4

What would you do next?

QUESTION 5

What will you discuss with Heath?

QUESTION 6

What other tests need to be performed now?

FURTHER INFORMATON

Heath seems shocked when you give him his HIV-positive result. You allow him some time to digest the information and advise him that people with HIV have normal lifespans with treatment (there are handouts for patients on the ASHM website).

He says that Josh drove up from Sydney yesterday and is waiting in the car. You ask him if he would like Josh to join the consultation. Heath looks relieved and says yes. Heath says it is ok to tell Josh his result.

QUESTION 7

What will you discuss with Heath and Josh?

CASE 6 ANSWERS

ANSWER 1

The differential diagnosis for Heath's rash could include the following:[1]

- Epstein-Barr virus (EBV)
- HIV seroconversion illness
- secondary syphillis
- acute hepatitis A or B
- parvovirus
- influenza
- cytomegalovirus
- toxoplasmosis
- pityriasis rosea
- viral exanthema (eg measles).

You are keen to exclude sexually transmissible infections (STIs), so you decide to take a brief sexual health history (refer to STI testing tool[1]). You ask Heath if he has a regular sexual partner. When he says no, you ask him whether he has had any casual sexual partners. He looks a bit uncertain and asks why you need to know this. You explain that his symptoms might be related to an STI and that you are just trying to determine if he is at risk. You reassure him that the consultation is confidential.

ANSWER 2

In planning testing for Heath at this time, testing recommendations for men who have sex with men (MSM) need to be considered. Heath qualifies for the annual MSM screening on the basis of having had sex with another man in the previous year. The following tests would be appropriate for Heath at this time:[2]

- full blood count (FBC)
- urea, electrolytes, creatinine (UEC)
- liver function tests (LFT)
- hepatitis A and B
- human immunodeficiency virus (HIV) antibody (Ab) –Ag
- gonorrhoea nucleic acid amplification test (NAAT)/culture (pharyngeal swab)
- gonorrhoea NAAT/culture and chlamydia NAAT (anal swab)
- chlamydia NAAT (first void urine, which is defined as the initial part of the urine stream, not the first urine of the day and not midstream urine)
- syphilis.

ANSWER 3

There is no longer a requirement for extensive pre-test counselling when contemplating HIV testing for a patient. However, some pre-test discussion is important.[3] As with any pathology test, explain to the person why the test is being done and how they will get the results. In this instance, because Heath is at high risk of a positive result, you ask him to make an appointment in a few days to give him the results.

The following day you receive a phone call from the lab: the preliminary HIV test is positive. The confirmatory western blot will take a few more days. Syphilis, hepatitis A, B and C and the other tests of the MSM screen are negative.

ANSWER 4

As you are based in a small, country town, you could call the sexual heath clinic in the regional town a few hours away and speak with a sexual health nurse.

In some jurisdictions, you will receive a phone call from a sexual health physician, who will talk you through the test results and advise you on what to do next. They may refer you to the Australasian Society of HIV Medicine (ASHM) website,[4] which contains several useful resources. On their advice, you ask your receptionist to change Heath's appointment to a long one at the end of your afternoon surgery.

ANSWER 5

The following points are appropriate and useful areas of discussion to have with Heath at this time and at future visits:

- The HIV Ab/Ag results are unconfirmed but likely to be true positive given the assessment (further confirmation will follow in the next week with the western blot result).
- What does a positive result mean?
- A discussion about test limitations and window periods for infection.
- Check Heath's understanding of HIV.
- Does he have any supports and who they are?
- Who will he tell about his HIV test result? Advise him to think carefully about this.
- The need for contact tracing of sexual partners, including Josh (refer to the Contact Tracing Tool[5]).
- Discuss the legal requirement in your state or territory to take all reasonable precautions to prevent transmission or to disclose his HIV status to sexual partners prior to sex.

People who have been recently diagnosed usually start treatment early, for their own benefit and to prevent transmission to others. You could reassure Heath that there is something he can do to manage his infection and that modern treatments have minimal side effects, are easy to take and are highly effective.

Contact tracing is a very important feature of good clinical practice in the management of patients diagnosed with STIs and tuberculosis, and forms the basis of control of these infections at the population level.[6] It may prevent re-infection in a given patient but also decreases the rate of STI transmission in the broader population. When discussing an STI diagnosis with a patient, GPs have a medicolegal responsibility to initiate a discussion with the patient about contact tracing. GPs should encourage patients to notify their contacts and provide support for this, for example, making use of the Let Them Know website (see Resouces for patients). Discussions and action plans should be documented in the patient's notes.[5]

Contact tracing can be performed through patient-initiated referral or via provider-initiated referral. Contact with past partners may be made by phone, sms, email, letter or in person. Briefly:

- **Patient-initiated referral** – the patient assumes responsibility for notifying contacts; GPs need to provide advice and guidance on what information should be provided to partners.
- **Provider-initiated referral** – healthcare professionals assume responsibility for notifying partners; in this model the GP, the GP's delegate (eg nurse) or another health agency informs the patient's contacts; the GP needs to obtain consent from the patient; the contact can be anonymous or not, depending on the wishes of the patient.[5]

The *Australasian Contact Tracing Manual* (see Resources for doctors) provides information on how far back to trace partners. Timeline recommendations are dependent on the nature of the infection. For HIV infection, current guidelines recommend starting with recent sexual or needle-sharing partners. The outer limit is the time of onset of risk behaviour or the last known negative HIV test result.[6] It would be appropriate to consider provider referral in HIV cases, given the higher morbidity experienced with this infection.[5]

Note that patients also need to contact trace partners with whom they have used a condom, as condoms do not offer equal protection against all STIs and need to be used carefully at all times, including

during foreplay and oral sex. Many STIs have no symptoms and previous partners may be inadvertently transmitting infection, not knowing that they are infected.[5]

ANSWER 6

As advised by the sexual health physician, additional tests that could be considered at this time include:

- a repeat HIV test
- a CD4 count and viral load
- viral resistance testing
- HLAB5701 testing for Abacavir hypersensitivity
- baseline toxoplasmosis IgG and cytomegalovirus IgG.3.

With regards to viral resistance testing, it was estimated in 2008 that 10–15% of HIV infections in Australia were due to a virus resistant to one or more classes of anti-retroviral treatments.[3]

ANSWER 7

It is important to encourage Josh to be tested (he had a STI screen at a sexual health clinic in Sydney a few years ago). Other points that could be raised in a joint discussion include:

- discussing the importance of avoiding sex or using condoms until Josh's results are available
- referring Heath to an HIV specialist in the regional centre
- providing Heath and Josh with HIV information sheets from the ASHM website or another appropriate source
- providing supportive counselling and/or referral for counselling (waiting for results can be a heightened period of anxiety).

REFERENCES

1. STI Testing tool. Clinical guidelines for the Management of STIs amongst priority populations. Available at www.stipu.nsw.gov.au/icms_docs/147045_GP_STI_Testing_Tool_2012.pdf [Accessed 10 February 2014).
2. Sexually transmitted infection testing guidelines for men who have sex with men. 2010. Available at www.stigma.net.au [Accessed 10 February 2014].
3. The National Management Guidelines For Sexually Transmissible Infections. 7th edn. Sexual Health Society of Victoria. Available at www.mshc.org.au/portals/6/nmgfsti.pdf [Accessed 10 February 2014].
4. Hoy J, Lewin S (eds). HIV Management in Australia – a guide for clinical care. Canberra: Australian Society of HIV Medicine, 2003. Available at www.ashm.org.au/images/Publications/Monographs/HIV_Management_Australasia/HIV-Management-Australia-2009.pdf [Accessed 10 February 2014].
5. General Practice New South Wales. STI Contact Tracing Tool for General Practice. Produced by NSW STIPU March 2011. Available at www.stipu.nsw.gov.au/content/Document/GP%20Contact%20Tracing%20Tool.pdf [Accessed 10 February 2014].
6. Australasian Society of HIV Medicine. Australasian Contact Tracing Manual. Available at ctm.ashm.org.au/Default.asp?PublicationID=6&sectionID=692 [Accessed 10 February 2014]

RESOURCES FOR PATIENTS

- Provides a range of useful patient STI fact sheets targeted to the public sector. www.stipu.nsw.gov.au/page/Public_Sector_Resources/STI_Fact_Sheets/
- Offers the option of notifying contacts via email, SMS or letter. Provides information on STIs and practical tips for patients. www.letthemknow.org.au.
- Website for MSM: provides information about STIs and offers the option of notifying contacts via email or SMS. www.thedramadownunder.info.
- Website for Aboriginal People: STI information, how & where to access STI Testing. Offers the option of notifying contacts anonymously via email or SMS. www.bettertoknow.org.au

RESOURCES FOR DOCTORS

- STI Clinical Management. This website provides a range of useful printable tools and guidelines for use in general practice. Available at www.stipu.nsw.gov.au/page/General_Practice_Resources/STI_Clinical_Management_2/
- Australasian Society of HIV Medicine (ASHM). ASHM is the peak Australasian organisation supporting the HIV, viral hepatitis and sexual health workforce. Available at www.ashm.org.au/default.asp?active_page_id=1
- Australasian Contact Tracing Manual. This provides information on how far back to trace, patient handouts, sample letters for clinicians and case studies. Available at ctm.ashm.org.au/Default.asp?PublicationID=6&sectionID=692
- Contact tracing interview video. mshc.org.au/healthpro/OnlineEducation/Videos/PartnerNotification/tabid/514/Default.aspx.
- STI Contact Tracing Tool for General Practice 2011.

INFECTIONS

In order to qualify for 6 Category 2 points for the QI&CPD activity associated with this unit:

- read and complete the unit of *check* in hard copy or online at the *gplearning* website at http://gplearning.racgp.org.au
- log into the *gplearning* website at http://gplearning.racgp.org.au and answer the following 10 multiple choice questions (MCQs) online
- complete the online evaluation.

If you are not an RACGP member, please contact the *gplearning* helpdesk on 1800 284 789 to register in the first instance. You will be provided with a username and password that will enable you access to the test.

The expected time to complete this activity is 3 hours.

Do not send answers to the MCQs into the *check* office. This activity can only be completed online at http://gplearning.racgp.org.au

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

FOR A FULL LIST OF ABBREVIATIONS AND ACRONYMS USED IN THESE QUESTIONS PLEASE GO TO PAGE 3.
FOR EACH QUESTION BELOW SELECT ONE OPTION ONLY.

QUESTION 1

Tuberculosis (TB) is rare in Australia but should always be considered as a possible diagnosis in people known to be from high-risk groups who present with symptoms suggestive of TB. Which of the following statements about the prevalence of TB is the most CORRECT?

A. High prevalence areas include Pakistan and Thailand.

B. High prevalence areas include Afghanistan, Bangladesh, India and the African continent.

C. High prevalence areas include Indonesia, Papua New Guinea and the Russian Federation.

D. A, B and C are correct.

E. A, B and C are incorrect.

QUESTION 2

Betty is 91 years of age and lives with her widowed daughter who is 62 years of age. Her daughter brought Betty to see you on a Monday morning to discuss their 'bad' weekend. Betty was unusually quiet and withdrawn over the weekend. Her daughter says that she has been restless, disorientated and terribly confused. She has had a low fever for which Betty has been taking paracetamol. Betty had poor sleep last night and there has been no improvement in her mental wellbeing today. Betty has a past history of hypertension and minor depression and recently she was diagnosed with mild cognitive impairment (MMSE 24). Your physical examination and a dipstick urinalysis indicate that Betty has a UTI. Which is the most CORRECT statement below?

A. Betty has signs of delirium, most likely due to her underlying UTI, and she should be prescribed trimethoprim 300 mg daily for 10 days.

B. Betty has signs of delirium, most likely due to her underlying UTI, and she should be prescribed trimethoprim 300 mg daily for 5 days.

C. Betty has signs of delirium, most likely due to her underlying UTI, and she should be prescribed cephalexin 500 mg 12-hourly for 10 days.

D. Betty has signs of delirium, most likely due to her underlying UTI, and she should be prescribed trimethoprim 300 mg daily for 3 days.

E. Betty has signs of delirium, most likely due to her underlying UTI, and she should be prescribed cephalexin 500 mg daily for 5 days.

QUESTION 3

Jennifer has been married to Anwar, who is originally from Somalia, for three years. They have just returned from overseas sabbatical overseas, working at the United Nations, and would like to start having a family. Jennifer has come to see you to request a pre-pregnancy health check. During the discussion she agrees to investigations including testing for blood-borne viral infections and sexually transmissible infections (STIs), as well as other appropriate tests (eg rubella titres). Which of the following statements is CORRECT?

A. Jennifer should be tested for HIV, chlamydia, syphilis and gonorrhoea.

B. Jennifer should be tested for HIV, hepatitis B and C, chlamydia, syphilis and gonorrhoea.

C. Jennifer should be tested for HIV, hepatitis C, chlamydia, syphilis and gonorrhoea.

D. Jennifer should be tested for HIV, hepatitis B, chlamydia, syphilis and gonorrhoea.

E. Jennifer should be tested for HIV, hepatitis A, B, C and D, chlamydia, syphilis and gonorrhoea.

QUESTION 4

Mabel, a pensioner aged 76 years, presents describing increased fatigue over several weeks and an irritating new-onset productive cough. She has not been able to get on with things and she feels foggy. She claims that she has had shortness of breath and chest discomfort/pain. She says she hasn't had a fever but that she has had 'shaking chills'. On examination her temperature is normal. She is currently being treated for hypertension and takes paracetamol occasionally for osteoarthritis. She has been a light smoker all her life. She had acute bronchitis this time last year and is worried that she has bronchitis again. Which one of the following statements is CORRECT?

A. Mabel has acute bronchitis and, as most bronchitis is viral in nature, she does not require antibiotics.

B. While the differential diagnosis for the presenting case should consider acute bronchitis and other respiratory conditions such as CAP, given her past history of bronchitis and presenting symptoms acute bronchitis is the most likely cause of Mable's illness.

C. The absence of fever excludes a diagnosis of CAP in Mable.

D. If Mabel reported night sweats and/or significant weight loss in addition to her current symptoms, bronchitis and CAP would still be likely diagnoses.

E. Mabel has some of the classic signs and symptoms of CAP, making bronchitis less likely, and should have antibiotics prescribed for her and a chest X-ray to confirm the diagnosis.

QUESTION 5

Lexie is a usually a boisterous, toilet-trained child aged 3.5 years. She presents with her mother who describes that Lexie has not been herself these past 2 days. She has been irritable and feverish on and off, and wet her pants yesterday. She has also indicated that it hurts to 'wee'. On examination, Lexie has a fever of 39.3ºC and complains of lower abdominal pain on palpitation. There are no other significant findings. Which of the following statements is CORRECT?

A. Lexie probably has a UTI; a urine sample should be taken for culture and empirical treatment with trimethoprim 4 mg/kg up to 150 mg, 6-hourly for 5 days could be commenced.

B. Lexie probably has a UTI; a urine sample should be taken for dipstick assessment and a sample should be sent for culture; empirical treatment with trimethoprim 4 mg/kg up to 150 mg, 12-hourly for 5 days could be commenced.

C. Lexie probably has a UTI; a urine sample should be taken for dipstick assessment and empirical treatment with trimethoprim 4 mg/kg up to 150 mg 12-hourly for 5 days could be commenced.

D. Lexie probably has a UTI; a urine sample should be taken for dipstick analysis and empirical treatment with trimethoprim 4 mg/kg up to 150 mg 6-hourly for 10 days could be commenced.

E. Lexie probably has a UTI, a urine sample should be taken for dipstick analysis and empirical treatment with trimethoprim 4 mg/kg up to 150 mg 12-hourly for 10 days could be commenced.

QUESTION 6

Within Australia hepatitis B is more prevalent in Aboriginal and Torres Straight Islander peoples, people who have injected drugs and in men who have sex with men. Which ONE of the following results is consistent with a diagnosis of chronic hepatitis B?

A. Hepatitis B surface antigen (HBsAg) negative; hepatitis B core antibody (anti-HBc) negative; hepatitis B surface antibody (anti-HBs) positive.

B. HBsAg negative; anti-HBc negative; hepatitis B surface antibody (anti-HBs) negative.

C. HBsAg negative; anti-HBc positive; anti-HBs negative.

D. HBsAg positive; anti-HBc negative; anti-HBs negative.

E. HBsAg positive; anti-HBc positive; anti-HBs negative.

QUESTION 7

Asymptomatic bacteriuria occurs frequently in the elderly and patients with urinary catheters. Which of the following statements about asymptomatic bacteriuria is CORRECT?

A. The prevalence of asymptomatic bacteriuria is reasonably high (15–50 %) among residential care residents.

B. The prevalence of asymptomatic bacteriuria is more common in people with severe cognitive impairment.

C. Asymptomatic bacteriuria should never be treated with antimicrobial therapy, as treatment has been implicated in the emergence of more resistant organisms.

D. Statements A and B.

E. Statements A, B and C.

QUESTION 8

In youngsters presenting with fever, correctly identifying the cause of fever and linking it to a UTI may prove challenging. Which one of the following statements is the most CORRECT?

A. A 5-month-old baby with fever (≥39.40ºC), vomiting and poor feeding has a UTI and a urine sample should be collected using the clean catch technique for testing.

B. A 5-month-old baby with fever (≥39.40ºC), vomiting and poor feeding probably does not have a UTI.

C. A 5-month-old baby with fever (≥39.40ºC), vomiting and poor feeding could have a UTI and should be referred for paediatric specialist review.

D. A 5-month-old baby with fever (≥39.40ºC), vomiting and poor feeding should be reviewed in 24 hours and treated with paracetamol.

E. A 5-month-old baby with fever (≥39.40ºC), vomiting and poor feeding should be treated empirically with oral antibiotics for a UTI while awaiting culture results.

QUESTION 9

Which of the statements is the most CORRECT regarding the management of CAP in community settings?

A. Amoxycillin 1 g orally, 8-hourly for 5–7 days and, in certain situations, procaine penicillin 1.5 g daily, intramuscular, can be substituted for amoxycillin.

B. Amoxycillin 1 g orally, 6-hourly for 3–5 days and, in certain situations, procaine penicillin 1.5 g daily, intramuscular, can be substituted for amoxycillin.

C. Amoxycillin 1 g orally, 8-hourly for 7–10 days and, in certain situations, procaine penicillin 1.5 g daily, intramuscular, can be substituted for amoxycillin.

D. Amoxycillin 1 g orally, 12-hourly for 5–7 days and, in certain situations, procaine penicillin 1.5 g daily, intramuscular, can be substituted for amoxycillin.

E. Amoxycillin 1 g orally, 6-hourly for 5–7 days and, in certain situations, procaine penicillin 1.5 g daily, intramuscular, can be substituted for amoxycillin.

QUESTION 10

Joseph, aged 36 years, is a single, bisexual musician, who is sexually active. He has had several male and female sexual partners over the past few months. He presented with a history of non-specific symptoms including fever and malaise. Following discussion, Joseph agreed to undergo the annual screening recommended for men who have sex with men. As a consequence of this testing Joseph was diagnosed as being HIV-positive. Which of the following statements is the most CORRECT with regards to the next steps that should be taken?

A. Contact tracing should be discussed and an agreement reached as to how this will be undertaken.

B. Contact tracing should be discussed and an agreement reached as to how this will be undertaken, as well as any legal requirement in his state or territory to take all reasonable precautions to prevent transmission and/or to disclose his HIV status to sexual partners prior to sex; discussions should be documented.

C. Joseph should be retested to confirm the diagnosis; contact tracing should be discussed as well as any legal requirement in his state or territory to take all reasonable precautions to prevent transmission and/or to disclose his HIV status to sexual partners prior to sex.

D. Joseph should be retested to confirm the diagnosis; contact tracing should be discussed and an agreement reached as to how this will be undertaken; discussions should be documented.

E. Contact tracing should be discussed and an agreement reached as to how this will be undertaken, as well as any legal requirement in his state or territory to take all reasonable precautions to prevent transmission and/or to disclose his HIV status to sexual partners prior to sex.

check

Independent learning program for GPs

check

Independent learning program for GPs

Unit 505 May 2014

Gastroenterology

RACGP

www.racgp.org.au/check

Subscriptions

For subscriptions and enquiries please call 1800 331 626 or email check@racgp.org.au

Published by

The Royal Australian College of General Practitioners
100 Wellington Parade
East Melbourne, Victoria 3002, Australia
Telephone 03 8699 0414
Facsimile 03 8699 0400
www.racgp.org.au

ABN 34 000 223 807
ISSN 0812-9630

check

Independent learning program for GPs

Gastroenterology

Unit 505 May 2014

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

ABOUT THIS ACTIVITY

Patients present with a range of gastrointestinal disorders in general practice settings. These include functional disorders, such as constipation or irritable bowel syndrome, and structural disorders where there is a bowel abnormality that often requires surgery. Food-borne disease is a common cause of self-limiting gastrointestinal problems. However, consumption of certain foods or components of foods (eg gluten) may lead to other more pressing problems that require medical management, such as allergies or coeliac disease. Alcohol consumption in excessive amounts and certain medications can lead to a number of wide-ranging gastrointestinal problems.

The focus on gastrointestinal problems in general practice also extends to prevention and guidelines, such as the *Guidelines for preventive activities in general practice* 8th edition (the Red Book),[1] which provide guidance for the prevention of common gastrointestinal cancers including oral cancer and colorectal cancer.

This unit of *check* considers gastrointestinal disorders presenting to general practice and discusses current options for management.

LEARNING OUTCOMES

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

- outline current diagnostic and management options for people with suspected coeliac disease
- explain the steps involved in *Helicobacter pylori* eradication for a patient diagnosed with an infection
- describe the pathophysiology, diagnosis and management of ascites
- describe the diagnosis and management of non-alcoholic fatty liver disease
- list considerations when planning travel advice for a patient.

AUTHORS

John Scally MBB,S DObst, RCOG, FRACGP, CTH was an examiner for the RACGP and contributor to *Therapeutic Guidelines: Gastrointestinal*. He has been in general practice for 40 years and has a special interest in travel medicine.

Peter Katelaris MBBS (Hons I), FRACP, FRCP, MD, AGAF is a senior consultant gastroenterologist at Concord Hospital in Sydney and Clinical Associate Professor at The University of Sydney. His main research interests are in acid-peptic disorders and, in particular, gastro-oesophageal reflux disease and *Helicobacter pylori* infection. Peter has conducted international collaborative research in the field and has been an invited speaker at international and regional meetings in many countries in Asia and Europe. He is currently an Australian representative to the Asia Pacific Association of Gastroenterology. He is an experienced clinician, researcher and educator. He has taught at all levels of medical education for many years.

Bambi Ward MBBS, FRACGP, Grad Dip Fam Med, MFam Med is an academic general practitioner with a special interest in coeliac disease. She currently works as a medical educator with Northern Territory General Practice Education (NTGPE) and is part of the NTGPE Medical and Cultural Educator team awarded the RACGP's National Faculty of Aboriginal and Torres Strait Islander Health Standing Strong Together Award in 2013. Bambi is a FRACGP examiner and is currently completing a PhD.

May Wong MBBS is a conjoint associate lecturer at the University of New South Wales and currently also works at Bankstown Lidcombe Hospital.

PEER REVIEWERS

Ashwin Garg BSc (Med) MBBS GradDipBiomedEng (UNSW) FRACGP DCH is a general practitioner working in a private practice in North Strathfield, Sydney.

Peter Bampton MBBS MD FRACP AGAF is Head of Luminal Gastroenterology, Department of Gastroenterology and Hepatology, Flinders Medical Centre, and Associate Professor of Gastroenterology, Flinders University of South Australia. He is a founding member of IBD Australia and Australian Neuro-gastroenterology and Motility Association, past chair of Digestive Health Foundation and member of council, Gastroenterological Society of Australia. Peter's areas of clinical interest include colorectal cancer screening, inflammatory bowel disease, colonic motility and clinical practice improvement.

REFERENCES

1. Britt H, et al. 2001. General practice activity in Australia 2000–01. AIHW Cat. No. GEP 8. Canberra: Australian Institute of Health and Welfare (General Practice Series No. 8).

GUIDE TO ABBREVIATIONS AND ACRONYMS IN THIS UNIT OF *CHECK*

ALT	alanine transaminase	HCC	hepatocellular carcinoma	NSAID	non-steroidal anti-inflammatory drug
AST	aspartate transaminase	IBS	irritable bowel syndrome	PCR	polymerase chain reaction PCR
BMI	body mass index	IgA	immunoglobulin A	SSRI	selective serotonin reuptake inhibitor
CRP	C-reactive protein	LFTs	liver function tests	tTG	transglutaminase antibody
DGP	deamidated gliaden peptide	MCS	microculture and sensitivity	UEC	urea, electrolytes creatinine
FBE	full blood examination	NAFLD	non-alcoholic fatty liver disease		
GGT	gamma glutamyl transpeptidase	NASH	non-alcoholic steatohepatitis		

CASE 1

JOHN IS TRAVELLING OVERSEAS

John, aged 39 years, has to travel to New Delhi, India, in March for 5 nights. The purpose of his trip is business in relation to his employment as a software consultant. He will attend meetings in an office environment during the day and most evenings he will be entertained by his hosts.

He attends for a pre-travel consultation. He is in good health and takes no medications.

QUESTION 1

What issues need to be addressed in such a consultation?

QUESTION 2

What specific advice would you give to John, who is in good health, for a 5-night business stay in New Delhi in March?

FURTHER INFORMATION

John sees you again 4 weeks after his return. The trip was successful but he developed severe diarrhoea on the last evening in New Dehli. John took the medications suggested and was able to fly home on his scheduled flight. He says he is much better but his bowels remain loose, windy and unpredictable.

QUESTION 3

How would you manage this presentation?

FURTHER INFORMATION

John does not have any other symptoms. There is no history of fever, rash, blood or mucus in the stools and systemically he is well. Examination is normal with no abdominal signs and no hepatomegaly.

QUESTION 4

Would you organise any laboratory investigations for John and, if so, what investigations would you request?

FURTHER INFORMATION

John's PCR results confirm the presence of *Giardia* and *Blastocystis*. His FBE, CRP and LFTs are normal.

QUESTION 5

How would you treat John considering these findings and the persistence of his symptoms?

QUESTION 6

Would you treat the *Blastocystis* infection?

FURTHER INFORMATION

You schedule a review in 3 months. John is now well but still has intermittent loose bowel actions associated with cramping abdominal pains.

QUESTION 7

What is John's diagnosis?

QUESTION 8

What do you advise John regarding further management?

CASE 1 ANSWERS

ANSWER 1

Advice needs to incorporate the following considerations[1]:

- destination
- duration of travel
- time of year
- activities to be undertaken
- personal health
- pregnancy, if appropriate
- age of the patient
- visiting friends and relatives
- travelling with children
- previous vaccinations (especially travel vaccinations) and any vaccination and medication allergies.

ANSWER 2

As well as addressing his individual considerations, John's consultation provides an opportunity to provide general information regarding health and travel. It also allows the GP an opportunity to review his current overall vaccination status with Australian guidelines.[2,3]

The provision of printed material is strongly recommended. This allows the GP to have a structure to refer to in the consultation and to be able to highlight the risks that John may encounter.

An excellent source for printing this information is wwwnc.cdc.gov/travel/destinations/list

John should be advised his health risks lie broadly in relation to food- and water-borne disease as well as vector-related illness. He should be reminded of the need for insurance, personal health and safety, and respect for cultural considerations. Recommendations for his 5-day business trip urban-based in India are:

- to be vaccinated against hepatitis A and typhoid

- to protect himself against mosquito borne disease, especially Dengue fever
- to be advised about prevention and treatment of traveller's diarrhoea
- to be aware of HIV/AIDS risk
- to avoid animal bites.

John's general vaccination status should be reviewed, especially hepatitis B, tetanus and pertussis. His measles immunity is important to determine for this destination. John may have a record of past illness or vaccination. If not, he should have his measles serology checked.

Medications for the treatment of diarrhoea that John could take with him include rehydration formula, loperamide and azithromycin. Azithromycin 500 mg tablets, 2 tabs stat, is recommended for most of Asia as the first step in the treatment of moderate-to-severe diarrhoea, as the prevalence of quinolone resistance to *Campylobacter* species is high. In Thailand, India and any other country with known high rates of quinolone resistance, azithromycin should be first-line therapy. Azithromycin is also the drug of choice for children and pregnant women.[4–6] Antibiotic prophylaxis for traveller's diarrhoea is not recommended for healthy travellers, including children.[5] Probiotics are not recommended for prevention of traveller's diarrhoea.[4]

Antimotility agents are useful for short-term management of diarrhoea during periods of inconvenience (eg travel, work). John should be provided with instructions on the use of loperamide (4 mg orally for the first dose, followed by 2 mg orally after each unformed stool, up to a maximum dose of 16 mg/day). Antimotility agents are not indicated for use in infants and children.[6,7]

The risk of insect-borne disease is low in the context of John's trip. Dengue fever is the highest risk, whereas malaria risk is low for New Delhi in March as that is the dry season and John is not scheduled to have outdoor exposure.[8–10]

Chikungunya exposure is through mosquito bite but is a lesser risk. This is more prevalent in Southern India and can be day and night exposure related.[11]

John should also be advised of the risk of animal bites (rabies) as well general travel risks of accidents, crime, jet lag, deep venous thrombosis and the need for insurance.[1]

Travellers should be advised to seek medical advice if they have a fever or are suffering from diarrhoea.[1]

John should consider carrying a letter from his GP detailing any prescription and over-the-counter medications he is carrying (such as loperamine, azithromycin, paracetamol) to avoid problems at customs.

ANSWER 3

A thorough history and examination are important. When assessing a person who has returned from an overseas trip, useful information to seek includes a complete travel history, including dates and places visited, potential exposure to disease (eg travel to rural areas, insect bites) as well as symptom onset.[12] John could be asked about possible exposure to or ingestion of contaminated food and water. Specifically, if he ate salads, had ice in drinks and/or consumed any raw food or dairy products. Examine John and note in particular whether he is febrile, jaundiced and whether there are abdominal signs, particularly hepatomegaly.

ANSWER 4

John should have a full blood examination (FBE) and C-reactive protein (CRP) measurement. In addition, liver function tests (LFTs), faeces microculture and sensitivity (MCS) and polymerase chain reaction (PCR) should be performed. LFTs are indicated to exclude underlying hepatitis (hepatitis E is to be considered in India).[1]

Faeces multiplex PCR is a new test to detect 10 pathogens:

- *Salmonella*
- *Campylobacter*
- *Shigella*
- *Yersinia*
- *Aeromonas*
- *Giardia*
- *Entamoeba*
- *Dientomoeba*
- *Blastocystis*
- *Cryptosporidium* species.

The advantage of the test is increased specificity and sensitivity as well as providing rapid (24-hour) results.[13] This is beneficial in deciding treatment and for public health notification in an outbreak setting.

ANSWER 5

Giardia is the most common gastrointestinal protozoan that causes chronic diarrhoea.[14] It is transmitted by the ingestion of food or water contaminated by faeces, by exposure to faecally contaminated surfaces and through person-to-person contact (including sexual contact).[15] Symptoms usually appear 1–2 weeks following infection and resolve within 2–4 weeks. Foul-smelling diarrhoea with greasy stools, abdominal cramps, bloating, flatulence and fatigue may be present, as well as anorexia and nausea. Fever and vomiting are uncommon but weight loss may occur.[15] In Australia, the treatment recommended for adults includes tinidazole 2 g orally as a single dose or metronidazole 2 g orally, daily for 3 days, or metronidazole 400 mg orally, 8-hourly for 5–7 days. Nitazoxanide 500 mg orally, 12-hourly for 3 days, is also an option; however, this drug is not currently registered in Australia and is only available through the Special Access Scheme.[14]

The clinical significance of *Blastocystis hominis* is contentious. Therapeutic guidelines suggest clinicians consider treatment with metronidazole or trimethoprim+sulfamethoxazole for symptomatic patients when other infectious/non-infectious causes have been excluded.[16]

You prescribe tinidazole 2 g stat for John's *Giardia* infection.

ANSWER 6

Treatment is not recommended for asymptomatic patients with *Blastocystis* on stool examination. However, it is recommended for symptomatic patients with *Blastocystis* when other infectious and non-infectious causes have been excluded.[16,17] Following discussion with John, who is symptomatic, you choose to treat John with the recommended dose[16] of metronidazole.

ANSWER 7

Following infection with *Giardia*, people may present with reactive arthritis, irritable bowel syndrome (IBS) or other chronic symptoms.[15] John most likely has post-infective IBS as he fulfils the diagnostic criteria outlined in *Table 1*[18]

Table 1: Rome III diagnostic criteria for IBS[18]

Criteria
Recurrent abdominal pain or discomfort (where discomfort means an uncomfortable sensation not described as pain) at least 3 days per month in the previous months that is associated with 2 of the following variables: • improvement with defecation • onset associated with a change in frequency of stool • onset associated with a change in form (appearance) of stool.
NOTE: Criteria must be fulfilled for the previous 3 months, with symptom onset at least 6 months prior to diagnosis. Adapted with permission from Clinical Infectious Diseases. © 2008 Infectious Diseases Society of America.

ANSWER 8

You advise John that your diagnosis needs to be confirmed by a gastroenterologist and provide him with a referral. He is likely to be symptomatic for months to years. Referral to a dietician would also be valuable for his ongoing management.

REFERENCES

1. Yung A, Ruff T, Torresi J, Leder K, O'Brien D. Manual of Travel Medicine: pre-travel guide for health care practitioners 2nd ed. Melbourne: IP Communications, 2011.
2. Immunise Australia. Available at www.immunise.health.gov.au [Accessed 10 April 2014].
3. Australian Government Department of Health. The Australian Immunisation Handbook 10 ed. Canberra: Commonwealth of Australia 2013. Available at www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/EE1905BC65D40BCFCA257B26007FC8CA/$File/handbook-Jan2014v2.pdf [Accessed 10 April 2014].
4. Australian Government, Department of Foreign Affairs and Trade. Travel advice: India. Available at www.smartraveller.gov.au/zw-cgi/view/Advice/India [Accessed 19 February 2014].
5. DuPont HL, Steffen R, eds. Textbook of travel medicine and health. Hamilton: BC Decker; 2001.
6. Centers for Disease Control and Prevention. Travellers Health: information for people travelling to India. Available at: wwwnc.cdc.gov/travel [Accessed 19 February 2014].
7. National Institute for Clinical Excellence. Diarrhoea – prevention and advice for travellers. Clinical Knowledge Summaries, 2013. Available at http://cks.nice.org.uk/diarrhoea-prevention-and-advice-for-travellers#!scenario [Accessed 22 April 2014].
8. Expert Group for Gastrointestinal Infections. Traveller's diarrhoea. In: eTG complete [Internet]. Melbourne: Therapeutic Guidelines Ltd, 2014: Available at www.tg.org.au [Accessed 19 February 2014].
9. O'Connor BA. Travelers' Diarrhea. Travelers' Health. Atlanta: Centers for Disease Control and Prevention, 2013; chapter 2. Available at wwwnc.cdc.gov/travel/yellowbook/2014/chapter-2-the-pre-travel-consultation/travelers-diarrhea [Accessed 20 March 2014].
10. Expert Group for Gastrointestinal Infections. Infectious diarrhoea: other supportive agents. In: eTG complete [Internet]. Melbourne: Therapeutic Guidelines Ltd, 2014. Available at www.tg.org.au [Accessed 19 February 2014].
11. Centers for Diseases Control and Prevention. Health information for travellers to India: clinician view. Available at wwwnc.cdc.gov/travel/destinations/clinician/none/india [Accessed 20 March 2014].
12. World Health Organisation. International Travel and Health Interactive. Countries or areas at risk. Available at http://apps.who.int/ithmap [Accessed 25 February 2014].
13. Centers for Disease Control and Prevention. Dengue Map. Available at www.healthmap.org/dengue/en [Accessed 25 February 2014].
14. Centres for Diseases Control and Prevention. Chikungunya fever. Geographic Distribution of Chikungunya virus (as of February 10, 2014). Available at www.cdc.gov/chikungunya/map/index.html [Accessed 19 February 2014].
15. Looke DF, Robson JM. Infections in the returned traveller. Med J Aust 2002;177:212–19.
16. McAuliffe GN, Anderson TP, Stevens M, et al. Systematic application of multiplex PCR enhances the detection of bacteria, parasites, and viruses in stool samples. J Infect 2013;67:122–29.
17. Expert Group for Gastrointestinal Infections. Giardia intestinalis (giardiasis). In: eTG complete [Internet]. Melbourne: Therapeutic Guidelines Ltd, 2014. Available at www.tg.org.au [Accessed 19 February 2014].
18. Gargano JW, Yoder JS. Travelers' Health: giardiasis. Atlanta: Centers for Disease Control and Prevention, 2013; chapter 3. Available at wwwnc.cdc.gov/travel/yellowbook/2014/chapter-3-infectious-diseases-related-to-travel/giardiasis [Accessed 24 February 2014].
19. Expert Group for Gastrointestinal Infections. Blastocystis hominis. In: eTG complete [Internet]. Melbourne: Therapeutic Guidelines Ltd, 2014. Available at www.tg.org.au [Accessed 19 February 2014].
20. Tan KSW. New insights on classification, identification and clinical relevance of *Blastocystis* spp. Clin Micro Revs 2008;21:639–35.
21. Dupont G. Postinfectious irritable bowel syndrome. Clin Infect Dis 2008;46:594–99. Available at http://cid.oxfordjournals.org/content/46/4/594.full [Accessed 20 March 2014].

RESOURCES FOR PATIENTS AND DOCTORS

- Superbug stowaways: multi-drug-resistant bacteria hitch a ride with travellers. NPSMedicineWise: Health News and Evidence 2014, www.nps.org.au/health-professionals/health-news-evidence/2014/superbug-stowaways?utm_source=nps-direct&utm_medium=email%20&utm_campaign=2014-2-iss16&hq_e=el&hq_m=332138&hq_l=14&hq_v=fce54abbbf
- James Cook University School of Public Health, Tropical Medicine and Rehabilitation Sciences. Useful links and databases for travel medicine and links to travel medicine clinics locally and overseas. Links to electronic journals of relevance to travel medicine are also provided, www.jcu.edu.au/phtmrs/abc/JCUPRD_047258.html
- Centre for Disease Control advice for clinicians, wwwnc.cdc.gov/travel
- World Health Organisation. Information regarding international travel and health, www.who.int/ith/en/
- Australian Federal Government, Department of Foreign Affairs and Trade. Travel-smart hints for Australian travellers and travel advice, information and to register travel, http://smartraveller.gov.au/tips/travel-smart.html
- Travel Medicine Alliance. General information and links to Australian government health advisories, general medical information for travellers and links to medical clinics in various countries, information on specific conditions and general information for travellers, www.travelmedicine.com.au/travel-health-information/resources
- Travel Clinics Australia: Fact Sheets. Travel fact sheets to help people plan their travel, www.travelclinic.com.au/fact-sheets-page

CASE 2

SAM HAS WEIGHT GAIN

Sam is a man aged 50 years who has elevated aspartate transaminase (AST) and alanine transaminase (ALT). Tests for viral hepatitis and autoimmune liver disease have been negative. His only symptom is occasional right upper quadrant pain. When asked about his alcohol intake he tells you that he does not consume alcohol. His weight has increased by 15 kg in the last 10 years and his body mass index (BMI) is 34.8 kg/m^2.

He has a medical history of hypertension and high cholesterol. He has a family history of diabetes and ischaemic heart disease but no liver disease. His only medication is rampiril. His physical examination is unremarkable and vital signs are normal. There are no peripheral stigmata of chronic liver disease. His liver span measures 18 cm and there is no splenomegaly.

The results of his initial serum investigations are shown in *Table 1*.

Table 1. Serum investigation results

	Sam's results	Reference values
Bilirubin	0.7 mol/L	2–20 mol/L
AST	68 U/L	10–45 U/L
ALT	120 U/L	5–40 U/L
Alkaline phosphatase	68 U/L	25–100 U/L
International normalised ratio (INR)	1.1	
Platelet count	389 x 10^9/L	150–400 x 10^9/L
Ferritin	285 µg/L	30–300 µg/L
Fasting glucose	9 mmol/L	3.0–6.0 mmol/L
Triglycerides	3.2 mmol/L	<2 mmol/L
HDL	1.2 mmol/L	>1 mmol/L
LDL	3.3 mmol/L	<2.5 mmol/L
Cholesterol	6.2 mmol/L	<5.5 mmol/L

In addition, a liver ultrasound showed a bright, enlarged liver, consistent with fatty infiltration.

QUESTION 1

What is the most likely cause of raised transaminases and fatty liver?

QUESTION 2

Sam asks you how he can have fatty liver disease despite not drinking any alcohol. How do you explain this to him?

QUESTION 3

Sam's wife is concerned that she may have fatty liver after she finds out about her husband's diagnosis. Would you recommend screening for her, even though she is asymptomatic?

QUESTION 4

What further work-up would you consider?

QUESTION 5

What radiographic finding would you expect with different imaging modalities?

QUESTION 6

What is the role of liver biopsy in the assessment of NAFLD?

FURTHER INFORMATION

A liver biopsy is performed for Sam and the findings are considered to be consistent with steatohepatitis.

QUESTION 7

Sam asks you about the therapeutic options for the management of NASH. What would you tell him?

CASE 2 ANSWERS

ANSWER 1

Non-alcoholic fatty liver disease (NAFLD) is a clinical histopathological entity with evidence of hepatic steatosis, either by imaging or by histology and, by definition, occurs in patients with little or no history of alcohol consumption. The disease ranges from fat accumulation in liver cells to a necro-inflammatory component, known as non-alcoholic steatohepatitis (NASH).

NASH is histologically indistinguishable from alcoholic steatohepatitis[1,2] and may progress to cirrhosis in up to 20% of patients.[3] NAFLD does not correlate with increased short-term morbidity or mortality; however, progression of this condition to NASH markedly increases the risks of cirrhosis, liver failure and hepatocellular carcinoma (HCC). Cirrhosis due to NASH is an increasingly frequent reason for liver transplantation.

The prevalence of NAFLD has doubled in last the 20 years, as have its major risk factors, which include central obesity, type 2 diabetes mellitus, dyslipidaemia and metabolic syndrome[4] (*Table 2*). The median estimate of the worldwide prevalence of NAFLD is 20% in the general population, making it the most common liver disorder in western industrialised countries.[4] The estimated prevalence of NASH is lower, ranging from 3–5%.[5]

Central obesity plus any two of four risk factors listed in *Table 2* constitute a diagnosis of metabolic syndrome. Central obesity is assessed by measuring the waist circumference (halfway between the lower rib cage and iliac crest). According to the International Diabetes Federation, central obesity is defined as a waist circumference >90 cm in males and >80 cm in females; different ethnic groups have different cut-points.

Table 2. Clinical identification of the metabolic syndrome[6]	
Risk factors	**Defining levels**
Elevated fasting triglycerides	≥150 mg/dL (1.7 mmol/L)
Reduced fasting HDL cholesterol	Male <40 mg/dL (1.03 mmol/L) Female <50 mg/dL (1.29 mmol/l)
Blood pressure	Systolic ≥130 mmHg Diastolic ≥85 mmHg
Fasting glucose	≥100 mg/dL (5.6 mmol/L)

Most patients with NAFLD are asymptomatic, although some may complain of fatigue, malaise and vague right upper abdominal discomfort.[7,8] A detailed patient history of alcohol consumption (threshold <20 g/day in women, <30 g/day in men) is critical, as no diagnostic test can reliably distinguish between alcoholic hepatic steatosis and NASH.[4]

Biochemically, patients with NAFLD may have mild-to-moderate elevations in transaminases,[7,8] although normal aminotransferase levels do not exclude NAFLD.[9,10] When elevated, the AST and ALT are typically 2–5 times the upper limit of normal, with an AST to ALT ratio of less than 1. Serum albumin and bilirubin levels are typically normal.

ANSWER 2

The pathogenesis of non-alcoholic fatty liver disease has not been fully elucidated. The most widely supported theory implicates insulin resistance as the key mechanism.[11] Others have proposed the 'multi-hit' hypothesis.[11] A combination of diet, obesity, insulin resistance and genetic predisposition leads to increased free fatty acids known as the 'first hit'. This sensitises the liver to injury from 'second hits' such as oxidative stress, inflammatory cytokines and mitochondrial dysfunction, leading to the necro-inflammatory component steatohepatitis and fibrosis. This results in reduced ability of mature hepatocytes to proliferate (*Figure 1*).

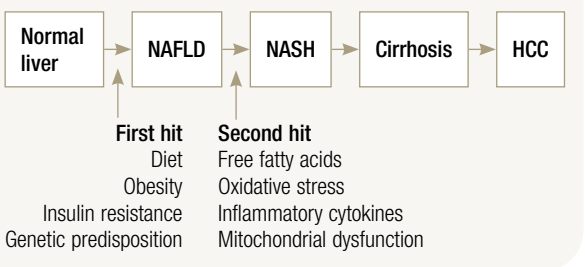

Figure 1. The multi-hit hypothesis (HCC = hepatocellular carcinoma)

Table 3 outlines the diagnostic requirement for a diagnosis of NAFLD.

Table 3. NAFLD diagnostic requirements[13]
Demonstration of hepatic steatosis by imaging or biopsy
Exclusion of significant alcohol consumption
Exclusion of other causes of hepatic steatosis
There are no co-existing causes for chronic liver disease

An alternative theory is that patients with the metabolic syndrome may have an over-accumulation of stored fat in the abdomen and liver (visceral fat), leading to NAFLD, which is the hepatic manifestation of the metabolic syndrome.[12]

ANSWER 3

Currently, the American Association for the Study of Liver Diseases guidelines do not recommend screening for NAFLD because there are uncertainties around which diagnostic test to use, how to treat NAFLD if discovered and whether screening is cost-effective.[13]

ANSWER 4

It is important to test all patients with hepatic steatosis for hepatitis infection to rule out this in patients with elevated aminotransferases and to determine immunity to guide future immunisations.[14] Sam has already tested negative for hepatitis. In addition to NAFLD, other causes of hepatic steatosis include alcoholic liver disease, hepatitis C, Wilson disease and starvation.[14] See *Table 4* for further tests.

Table 4. Tests to consider to exclude other causes of hepatic disease and steatosis[15,16]
Anti-hepatitis C virus antibody
Hepatitis A IgG
Hepatitis B surface antigen
Plasma iron, ferritin, and total iron binding capacity
Serum gamma-globulin level, antinuclear antibody, anti-smooth muscle antibody, and anti-liver/kidney microsomal antibody-1

ANSWER 5

Radiographic findings include a hyperechoic texture or a bright liver because of diffuse fatty infiltration on ultrasound, owing to increased acoustic interfaces because of intracellular accumulation of lipid vesicles. There is decreased hepatic attenuation on computed tomography, and an increased fat signal on magnetic resonance imaging. However, no imaging modality is able to differentiate between the histologic subtypes of NAFLD and NASH.[17] Magnetic resonance spectroscopy has the advantage of being quantitative and may be particularly helpful in patients with small amounts of hepatic steatosis, but it is not widely available.[18]

ANSWER 6

Liver biopsy is the gold standard for diagnosing NAFLD but in many cases a reasonable diagnosis can be made on the basis of the patient's history, laboratory tests and imaging findings, provided other disorders have been excluded.[4] The disadvantages of biopsy are cost, sampling error and procedure-related morbidity and mortality.

Some patients will continue to have an unclear diagnosis following a non-invasive evaluation and in such cases, a liver biopsy is indicated. In addition, liver biopsy is the only method currently available to differentiate between NAFLD and NASH. Furthermore, it can be used to grade the severity of NASH to guide patient care and may also motivate patients to enact lifestyle modifications.[4] For example, those found

to have cirrhosis will require screening for oesophageal varices and hepatocellular carcinoma (HCC), whereas patients with early fibrosis may be motivated to lose weight. Histological findings in NAFLD include steatosis (typically macrovesicular) with or without lobaular and portal inflammation, whereas in NASH there is also hepatocyte injury (typically ballooning degeneration) with or without fibrosis. Situations where a biopsy should be considered are outlined in *Table 5*.

Table 5. Scenarios when a liver biopsy should be considered[19]

Biochemical or clinical findings	Features suggestive of…
Serum ferritin >1.5 times the upper limit of normal >45 years of age with associated obesity or diabetes	NASH and advanced fibrosis
Peripheral stigmata of chronic liver disease Splenomegaly Cytopaenias (suggestive of cirrhosis)	Cirrhosis

Non-invasive methods for assessment of fibrosis rely on two different, but complementary, approaches: serum biomarkers of hepatic inflammation and transient elastography to measure liver stiffness, where an ultrasound pulse wave is transmitted through the liver and the wave velocity correlates with liver stiffness.[20]

The NAFLD Activity Score (NAS) is a new histopathological scoring system for NASH activity that ranges from 0–8 and assesses steatosis, lobular inflammation and hepatocyte ballooning. It is currently used in clinical trials. An NAS >5 indicates definite steatohepatitis.[21]

ANSWER 7

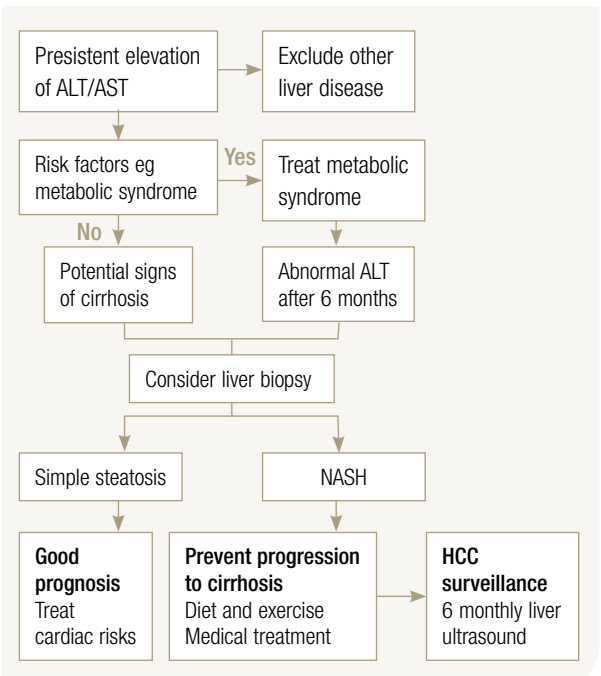

Figure 2. Proposed algorithm for management of NAFLD/NASH

At the present time, there is no evidence-based approved drug therapy.[4] A proposed management algorithim is shown in *Figure 2*. Lifestyle change is critical in any attempt to reverse the course of NASH.[13] NASH should be treated aggressively to prevent progression to cirrhosis, as these patients are frequently not candidates for liver transplantation because of their morbid obesity, cardiovascular disease or other complications of their underlying condition.[13] The goals of treatment for NASH are therefore to reduce the histological features and improve insulin resistance and liver enzyme levels.[13]

Proper control of diabetes, hyperlipidaemia and cardiovascular risks is recommended,[4,14] and referral to a dietician could be considered. Studies with atorvastatin and pravastatin have shown improvement in histology in patients with NASH.[22,23] NAFLD patients with dyslipidaemia should be treated with statins. Patients with underlying liver disease do not seem to have any additional risk of statin toxicity and serious hepatotoxicity from statins is rare.[14]

The overall goal of lifestyle change is to reduce excess weight; even a gradual 5–10% weight loss has been shown to improve liver histology and enzymes.[24] This is usually most successful if combined with a regular exercise program and elimination of a sedentary lifestyle. Drugs targeting insulin resistance, such as thiazolidinediones and metformin, are approved for diabetes but not for NAFLD/NASH, and should be considered experimental/off-label.[13] Foregut bariatric surgery may be beneficial for patients with morbid obesity.

CONCLUSION

A fasting glucose test confirmed a new diagnosis of diabetes mellitus. Sam was referred to an exercise physiologist and dietitian who prescribed a graded exercise program in combination with caloric restriction. This resulted in weight loss of more than 15 kg over 6 months. This weight loss was maintained for a further 6 months. His transaminase, glucose and lipid levels normalised without pharmacological intervention. A repeat liver biopsy 12 months after the initial biopsy demonstrated improved histology.

REFERENCES

1. Ludwig J, Viggiano TR, McGill DB, Oh BJ. Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. Mayo Clin Proc 1980;55:434–38.
2. Sheth SG, Gordon FD, Chopra S. Nonalcoholic steatohepatitis. Ann Intern Med 1997;126:137–45.
3. Matteoni CA, Younossi ZM, Gramlich T, Boparai N, Liu YC, McCullough AJ. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. Gastroenterology 1999;116:1413–19.
4. Farrell G. Fatty liver disease. Sydney: Digestive Health Foundation, 2007. Available at: www.gesa.org.au/files/editor_upload/File/Professional/Fatty-Liver-1st-Edition.pdf [Accessed 25 February 2014].
5. Amarapurkar D, Kamani P, Patel N, et al. Prevalence of nonalcoholic fatty liver disease: population based study. Ann Hepatolo 2007;6:161–63.
6. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and Management of the Metabolic Syndrome: An American Heart Association/National Heart, Lung and Blood Institute Scientific Statement. Circulation 2005;112:2735–52. Available at http://circ.ahajournals.org/content/112/17/2735.full.pdf+html [Accessed 25 February 2014].

7. Farrell GC, Wong VW, Chitturi S. NAFLD in Asia – as common and important as in the West. Nat Rev Gastroenterol Hepatol 2013;10:307–18.
8. Bacon BR, Farahvash MJ, Janney CG, Neuschwander-Tetri BA. Nonalcoholic steatohepatitis: an expanded clinical entity. Gastroenterology 1994;107:1103–09.
9. Charatcharoenwitthaya P, Lindor KD, Angulo P. The spontaneous course of liver enzymes and its correlation in nonalcoholic fatty liver disease. Dig Dis Sci 2012;57:1925–31.
10. Mofrad P, Contos MJ, Haque M, et al. Clinical and histologic spectrum of nonalcoholic fatty liver disease associated with normal ALT values. Hepatology 2003;37:1286–92.
11. Polyzos SA, Kountouras J, Zavos C. Non-alcoholic fatty liver disease: the pathogenic roles of insulin resistance and adipocytokines. Curr Mol Med 2009:9:299–314.
12. Jeong SK, Kim YK, Park JW, Shin YJ, Kim DS. Impact of visceral fat on the metablic syndrome and nonalcoholic fatty liver disease. J Korean Med Sci 2008;23:789–95. Available at www.ncbi.nlm.nih.gov/pmc/articles/PMC2580019/ [Accessed 16 April 2014].
13. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. Hepatology 2012;55:2005–23.
14. Iser D, Ryan M. Fatty liver disease. Aust Fam Phys 2013:42:444–47
15. Friedman S, Schiano T. Cirrhosis and its sequelae. In: Goldman L, Ausiello D, eds. Cecil Textbook of Medicine. 22nd ed. Philadelphia, Pa.: Saunders, 2004:936–44.
16. Crawford JM. Liver and biliary tract. In: Kumar V, Abbas AK, Fausto N, eds. Robbins and Cotran Pathologic Basis of Disease. 7th ed. Philadelphia, Pa.: Elsevier Saunders, 2005:877–938.
17. Schwenzer NF, Springer F, Schraml C, Stefan N, Machann J, Schick F. Non-invasive assessment and quantification of liver steatosis by ultrasound, computed tomography and magnetic resonance. Hepatology 2009;51:433–35.
18. Szczepaniak LS, Nurenberg P, Leonard D, et al. Magnetic resonance spectroscopy to measure hepatic triglyceride content: prevalence of hepatic steatosis in the general population. Am J Physiol Endocrinol Metab 2005;288:E462–68.
19. Rockey DC, Caldwell SH, Goodman ZD, Nelson RC, Smith AD. AASLD position paper: liver biopsy. Hepatology 2009;49:1017–44.
20. Rockey DC, Bissell DM. Noninvasive measures of liver fibrosis. Hepatology 2006;43(2 Suppl 1):S113–20.
21. Brunt EM, Kleiner DE, Wilson LA, Belt P, Neuschwander-Tetri BA. Nonalcoholic fatty liver disease (NAFLD) activity score and the histopathologic diagnosis in NAFLD: distinct clinicopathologic meanings. Hepatology 2011;53:810–20.
22. Hyogo H, Tazuma S, Arihiro K, et al. Efficacy of atorvastatin for the treatment of nonalcoholic steatohepatitis with dyslipidemia. Metabolism 2008;57:1711–18.
23. Rallidis LS, Drakoulis CK, Parasi AS. Pravastatin in patients with nonalcoholic steatohepatitis: results of a pilot study. Atherosclerosis 2004;174:193–96.
24. Promrat K, Kleiner DE, Niemeier HM, et al. Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. Hepatology 2010;51:121–29.

CASE 3

JAMES PRESENTS WITH ABDOMINAL SYMPTOMS

James is 55 years of age. For the past 2 weeks he has been having nausea, vomiting, lower abdominal cramps without diarrhoea, and he has lost weight. His medical history is otherwise non-contributory.

QUESTION 1

While you are taking James's history he mentions that since his wife's death 9 years ago, he drinks everyday. How could you ask James about his alcohol consumption?

FURTHER INFORMATION

You conduct a physical examination, which shows James is cachectic and in moderate respiratory distress, but alert and oriented to time, date and place. He has three spider angiomas on his upper chest. Abdominal examination reveals prominent veins on a very tense abdomen. The liver edge is percussed below the right costal margin and there is no ascites (accumulation of fluid in the peritoneal cavity). The spleen cannot be palpated. Cranial nerves II–XII are grossly intact but there is impaired vibratory sensation of the lower extremities.

QUESTION 2

On the basis of the physical examination, you order a blood test to investigate James's liver function (*Table 1*). How would these results inform your diagnosis?

Table 1. James's blood test results

	James results	Reference ranges
Bilirubin	16	2–17 µmol/L
Albumin	23	35–55 g/L
Aspartate aminotransferase (AST)	37	10–45 U/L
Alanine aminotransferase (ALT)	280	5–40 U/L
Gamma glutamyl transpeptidase (GGT)	137	5–51 U/L
Alkaline phosphatase	954	25–100 U/L

FURTHER INFORMATION

You explain that liver damage resulting from chronic heavy alcohol consumption can manifest as fatty liver, alcoholic hepatitis and cirrhosis. However, you tell James that the assumption that alcoholic liver disease always progresses linearly from alcoholic fatty liver to alcoholic hepatitis and, ultimately, to cirrhosis is not correct.

QUESTION 3

What are the signs and symptoms of alcoholic liver disease and chronic liver disease?

QUESTION 4

How would you manage James's alcoholic liver disease?

QUESTION 5

Are there any specific measures that could be taken to support James' nutrition?

FURTHER INFORMATION

James returns to see you 6 months later with bilateral swelling of his legs, increased distension of his abdomen and yellowing of his skin and the sclera of his eyes.

QUESTION 6

What questions would you ask James to help clarify the cause of his ascites?

QUESTION 7

What investigations would you perform?

FURTHER INFORMATION

James has a liver ultrasound, which confirms a cirrhotic liver.

QUESTION 8

What are the implications for James? What are the long-term management goals for cirrhosis?

CASE 3 ANSWERS

ANSWER 1

Obtaining an accurate history of alcohol use is of prime importance. Questioning the patient's family in private, after receiving permission from the patient to discuss their care with family members, may help extract information about the patient's alcohol use.

Alcohol intake is recorded in standardised units; in Australia, one standard drink contains 10 g of alcohol. The volume of a standard drink varies depending on the alcohol concentration of the beverage. For example, a standard drink of beer (4.8% alcohol) is about 285 ml, whereas a standard drink of wine (11.5% alcohol) is about 100 ml.[7]

Information about alcohol consumption obtained from the patient or their family can be supplemented by use of either the CAGE[8] (*Table 2*) or AUDIT[9–11] (*Table 3*) questionnaires, which may assist in establishing the likelihood of problem alcohol drinking. AUDIT is a 10-item questionnaire that is easy for patients to complete and for health professionals to score. AUDIT-C is a 3-item alcohol screen where a score of 4 or more in men or 3 or more in women is considered positive for identifying hazardous drinking or active alcohol use disorders.[12]

Table 2. Cage questionnaire[8]

C	Have you felt the need to **C**ut down?
A	Have you felt **A**nnoyed at the suggestion that you might have an alcohol problem?
G	Have you felt **G**uilty about excessive drinking?
E	Do you need an **E**ye opener in the morning?
Score 1 for each positive response; scores of 2 or more suggest an alcohol problem	

Table 3. Audit-C questionnaire

1. How often do you have a drink containing alcohol?				
Never	Monthly or less	2–4 times a month	2–3 times a week	4 or more times a week
0	1	2	3	4
2. How many drinks containing alcohol do you have on a typical day when you are drinking?				
1 or 2	3 or 4	5 or 6	7–9	10 or more
0	1	2	3	4
3. How often do you have six or more drinks on one occasion?				
Never	Less than monthly	Monthly	Weekly	Daily or almost daily
0	1	2	3	4

ANSWER 2

Aminotransferase abnormalities, generally <300 IU/L, are common in alcoholic liver disease. Although not seen in James's blood test results, a disproportionate increase in serum AST, compared with ALT, is highly suggestive of alcoholic liver injury, especially if the ratio of AST:ALT is >2.0. GGT is involved in the uptake of amino acids and is raised in chronic alcohol users.[2] Thrombocytopaenia may result from primary bone marrow hypoplasia and/or splenic sequestration due to portal hypertension and an enlarged spleen. Macrocytosis (determined by an elevated mean corpuscular volume) suggests longstanding disease and may reflect poor nutritional status, vitamin B12 or folate deficiency, alcohol toxicity and/or increased lipid deposition in red cell membranes.[3]

Patients may have low serum albumin levels caused by malnutrition and decreased synthesis in the setting of hepatic dysfunction. Iron absorption, synthesis, and uptake through liver receptors and mediators are diminished because of liver impairment. Ferritin synthesis, which occurs in the liver, is decreased in people with liver cirrhosis.[4]

If alcoholic hepatitis is suspected, it is important to check for leukocytosis as the magnitude of the white blood cell elevation correlates closely with the severity of the hepatic injury.[5] Furthermore, elevated bilirubin, hypoalbuminaemia and prolonged prothrombin levels are important indicators of severity.[6]

ANSWER 3

Early alcoholic liver disease may present with few signs and symptoms.[13] Patients may present with non-specific digestive tract symptoms such as nausea, dry retching, diarrhoea, anorexia and abdominal pain.[14] Patients may also seek medical attention because of the consequences of alcoholism, which may include accidents, violent behavior, depression, tremors, poor work performance or social disruptions. Late signs specific for alcoholic liver disease include Dupuytren contracture, parotidomegaly and proximal myopathy. Exocrine pancreatic failure from alcohol-induced chronic pancreatitis may result in pale, fatty motions that are difficult to flush.[15]

Complications of chronic liver disease may present with signs of portal hypertension, including splenomegaly, collateral veins and ascites. As the liver is responsible for the production of coagulation factors, the patient may bruise easily.[15] Patients are often malnourished, which manifests as proximal muscle wasting and decreased grip strength. Palmar erythema, spider naevi, gynecomastia, decreased body hair and testicular atrophy are thought to result from decreased hepatic metabolism and clearance of androstenedione, allowing increased peripheral conversion to estrogen.[16] Oedema, ascites and hepatic encephalopathy result from hepatocellular insufficiency and portal hypertension. In a patient with ascites, physical examination findings may include abdominal distention, bulging flanks, shifting dullness and a fluid wave. If the liver is not palpable, remember that it can be small, so continue percussing for the lower border of the liver above the costal margin.

ANSWER 4

Abstinence from alcohol and good nutrition are pivotal in the management of alcoholic liver disease as continued use of alcohol is associated with progression of disease.[17,18] Other important aspects of management include care when prescribing medications,

ensuring immunisations are up to date (eg pneumococcal, meningococcal, influenza, hepatitis A and B) and early referral for complications. It is particularly important to counsel individuals who are hepatitis C positive about avoiding alcohol because alcohol adds to the risk of developing hepatocellular cancer.[18]

In patients who have not yet progressed to cirrhosis, abstinence may allow for reversal of the alcohol-induced changes in the liver.[19] Simple, uncomplicated fatty liver is usually asymptomatic and self-limiting. It is estimated that 8–20% of patients with alcoholic fatty liver will develop alcoholic cirrhosis.[20] In patients with cirrhosis, alcohol abstinence decreases the risk of hepatic decompensation and improves survival. There is histological improvement, decreased rates of progression of cirrhosis, reductions in portal pressure, decreased rebleeding from varices and improved survival.[21,22]

Patients should be referred for treatment for alcohol abuse or dependence to increase the likelihood of successful abstinence.[10] Pharmacological therapy with agents such as baclofen may aid with abstinence.[23,24] Since many people with alcoholic liver disease have a long history of heavy alcohol use, they are at risk for alcohol withdrawal.[10]

ANSWER 5

All patients with alcoholic liver disease should undergo a nutritional assessment[17] because protein, carbohydrate and lipid metabolism are all affected by liver disease. Patients with alcoholic fatty liver who are not malnourished and do not have evidence of vitamin or mineral deficiencies should be encouraged to eat a healthy, balanced diet.

Nutritional support includes providing adequate calories and protein, as well as vitamins (eg thiamine, folate, and pyridoxine) and minerals (eg phosphate, magnesium) repletion.[25] Vitamin K is often ineffective because the coagulopathy is more a reflection of underlying liver failure than vitamin K deficiency.[26]

The American Association for the Study of Liver Diseases and the American College of Gastroenterology recommend that patients with alcoholic cirrhosis should eat several times per day, including breakfast and a night-time snack, which helps prevent the breakdown of muscle stores overnight.[17] To prevent Wernicke-Korsakoff syndrome, thiamine supplementation should be offered to people with alcoholic liver disease who cannot stop drinking).[9] Patients who develop ascites should be advised to avoid salt, including foods with a high salt content and the addition of salt to meals.[18]

ANSWER 6

Questions regarding the onset of symptoms may be useful for distinguishing between obesity and ascites. Patients generally seek medical advice early, within a few weeks of ascites presenting, as fluid usually accumulates rapidly and patients are intolerant of the distension and associated early satiety and shortness of breath. Conversely, the thickening abdominal wall and other signs associated with obesity develop over a longer period of time (months or years).

ANSWER 7

Physical examination and abdominal imaging, most often ultrasonography, will confirm the diagnosis of ascites. The overall accuracy of physical examination (and its findings) is dependent on a number of variables, including the amount of fluid present and examination technique. An important finding on physical examination that helps confirm ascites is detection of flank dullness. Shifting dullness with rotation of the patient may also be observed. The absence of flank dullness on physical examination is consistent with no ascites being present, with an accuracy of over 90%.[27]

Ascites suspected on the basis of history and physical examination should be confirmed with radiographical imaging.[28] Ultrasonography can detect fat in the liver, increased echogenicity of liver cirrhosis, splenomegaly and varices when portal hypertension develops, and the less common complication of hepatocellular carcinoma. It can also confirm the presence of ascites and show any fluid that might be located in discrete areas of the peritoneal cavity. It is an important investigation and may obviate the need for liver biopsy. Calcification of the pancreas can occur in alcohol-induced chronic pancreatitis. In patients with cirrhosis and portal hypertension, an ultrasound may show dilatation of veins, including the portal vein, to ≥13 mm, dilation of the splenic and superior mesenteric veins to ≥11 mm, as well as reduction in portal venous blood flow velocity, splenomegaly (diameter >12 cm) and recanalisation of the umbilical vein.[29] An ultrasound may also reveal evidence of hepatocellular carcinoma, which can be further evaluated with computed tomography (CT) or magnetic resonance imaging (MRI).

The ascitic fluid should be sent for analysis of appearance, cell count and differential diagnosis, as well as culture. Cirrhotic ascites has the characteristics of a transudate with a gap of more than 11 g/L between the serum and ascitic concentrations of albumin. The presence of an exudate (<11 g/L) can indicate complications such as spontaneous bacterial peritonitis or hepatocellular carcinoma, or that another disease process (eg malignancy, pancreatitis or tuberculosis) may be causing the ascites.[30]

Alpha fetoprotein could be considered as an adjunct to ultrasonography for hepatocellular carcinoma screening in patients with alcoholic cirrhosis.

ANSWER 8

Alcoholic cirrhosis represents a late stage of progressive liver damage whereby the hepatic architecture is distorted by fibrosis, which replaces hepatocytes, and the formation of regenerative nodules. It is usually irreversible in its advanced stages at which point the only option may be liver transplantation. Complications that are best treated by early referral to specialist care include variceal haemorrhage, ascites, neuropsychiatric complications and unexplained deterioration.[31] Unexplained deterioration may indicate the development of complications such as spontaneous bacterial peritonitis or hepatocellular carcinoma. Once these complications develop, patients are considered to have decompensated cirrhosis.

Portal hypertension is a major complication of cirrhosis. It arises when there is resistance to portal blood flow within in the liver due to

structural changes (eg fibrosis) and dynamic changes (eg increased vascular tone).[32] It leads to fluid retention and, ultimately, ascites in patients with cirrhosis. Ascites is problematic on many levels: directly, by causing symptoms of abdominal discomfort and early satiation; and indirectly, by facilitating complications of infections and multi-organ dysfunction such as spontaneous bacterial peritonitis and hepatorenal syndrome.[33]

The treatment approach in patients with ascites includes restricting dietary sodium intake, avoiding sodium-retaining drugs and performing large-volume paracentesis.[33] However, paracentesis should be reserved for patients with tense or refractory ascites and diuretic therapy should be initiated immediately after the procedure. Most patients are started on a combination diuretic regimen with frusemide and spironolactone, titrated to achieve a maximal weight loss of 0.5 kg/day, but this should be done in consultation with a gastroenterologist.[30]

REFERENCES

1. Australian Government Department of Health and Ageing. New national guidelines for alcohol consumption. Canberra: Commonwealth of Australia, 2013. Available at www.alcohol.gov.au/internet/alcohol/publishing.nsf/Content/36E6FEE732C8DF1BCA25767200769CD8/$File/adult.pdf [Accessed 25 March 2014].
2. Nishimura N, Teschke R. Alcohol and gamma-glutamyltransferase. Klin Wochenschr 1983;61:265–75.
3. Marayama S, Hirayama C, Yamamoto S, et al. Red blood cell status in alcoholic and non-alcoholic liver disease. J Lab Clin Med 2001;138:332–37.
4. Büyükaşik NS, Nadire I, Akin FE, et al. Serum iron parameters in cirrhosis and chronic hepatitis: detailed description. Turk J Gastroenterol 2011;22:606–11.
5. Amini M, Runyon BA. Alcoholic hepatitis 2010: a clinician's guide to diagnosis and therapy. World J Gastroenterol 2010;16:4905–12.
6. Udell JA, Wang CS, Tinmouth J, et al. Does this patient with liver disease have cirrhosis? JAMA 2012;307:832–42.
7. Australian Government Department of Health. The Australian standard drink. Available at www.alcohol.gov.au/internet/alcohol/publishing.nsf/Content/standard [Accessed 25 March 2014].
8. Ewing JA. Detecting alcoholism. The CAGE questionnaire. JAMA 1984;252:1905–07.
9. National Institute of Health and Clinical Excellence. Alcohol use disorders: preventing harmful drinking: quick reference guide. London: NICE Public Health Guidance 24, 2010. Available at www.nice.org.uk/nicemedia/live/13001/49024/49024.pdf [Accessed 4 March 2014].
10. Australian Government Department of Health and Ageing. Quick reference guide to the treatment of alcohol problems. Canberra: Commonwealth of Australia, 2009. Available at www.alcohol.gov.au/internet/alcohol/publishing.nsf/Content/864FDC6AD475CB2CCA257693007CDE3A/$File/treatqui.pdf [Accessed 25 March 2014].
11. Saunders JB, Aasland OG, Babor TF, et al. Development of the alcohol use disorders identification test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption–II. Addiction 1993;88:791–804.
12. Babor TF, Higgins-Biddle JC, Saunders, JB, Monteiro MG. Audit: the Alcohol Use Disorders Identification Test : guidelines for use in primary health care, 2nd edition. Geneva: World Health Organization, 2001.
13. Better Health Channel. Know the facts: alcohol and the liver. State Government Victoria, 2012. Available at: www2.betterhealth.vic.gov.au/saywhen/know-the-facts/consequences-of-drinking-alcohol-and-the-liver [Accessed 25 March 2014].
14. Diehl AM. Liver disease in alcohol abusers: a clinical perspective. Alcohol 2002;27:7–11.
15. Talley N. O'Conner S. Clinical Examination. A systematic guide to physical diagnoses. 6th edn. Sydney: Churchill Livingstone; 2009.
16. Gordon GG. Conversion of androgens to estrogens in cirrhosis of the liver. Clin Endocrinol Metab 1975;40:1018–26.
17. O'Shea RS, Darasathy S, McCullough AJ. Alcoholic Liver Disease. Hepatology 51:307–28.
18. Duggan AE, Duggan JM. Alcoholic liver disease: assessment and management. Aust Fam Physician 2011:590–03.
19. Pessione F, Ramond MJ, Peters L, et al. Five-year survival predictive factors in patients with excessive alcohol intake and cirrhosis. Effect of alcoholic hepatitis, smoking and abstinence. Liver Int 2003;23:45–53.
20. Borowsky SA, Strome S, Lott E. Continued heavy drinking and survival in alcoholic cirrhotics. Gastroenterology 1981;80:1405–09.
21. Cuthbert JA, Arslanlar S, Yepuri J, Montrose M, Ahn CW, Shah JP. Predicting Short-Term Mortality and Long-Term Survival for Hospitalized US Patients with Alcoholic Hepatitis. Dig Dis Sci 2014; (epub ahead of print).
22. Raynard B, Balian A, Fallik D, et al. Risk factors of fibrosis in alcohol-induced liver disease. Hepatology 2002;35:635–38.
23. Addolorato G, Leggio L, Ferrulli A, et al. Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study. Lancet 2007;370:1915–22.
24. Forrest EH, Evans CD, Stewart S, et al. Analysis of factors predictive of mortality in alcoholic hepatitis and derivation and validation of the Glasgow alcoholic hepatitis score. Gut 2005;54:1174–79.
25. Mendenhall CL, Anderson S, Weesner RE, Goldberg SJ, Crolic KA. Protein-calorie malnutrition associated with alcoholic hepatitis. Veterans Administration Cooperative Study Group on Alcoholic Hepatitis. Am J Med 1894;76:211–22.
26. Saja MF et al. The coagulopathy of liver disease: does vitamin K help? Blood Coagul Fibrinolysis 2013;24:10–17.
27. Cattau EL Jr, Benjamin SB, Knuff TE, Castell DO. The accuracy of the physical examination in the diagnosis of suspected ascites. JAMA 1982;247:1164–66.
28. Runyon BA. Evaluation of adults with ascites. UpTodate 2014: Topic 1261 Version 19.0. Available at www.uptodate.com/contents/evaluation-of-adults-with-ascites [Accessed 5 March 2014].
29. Berzigotti A, Ashkenazi E, Reverter E, Abraldes JG, Bosch J. Non-invasive diagnostic and prognostic evaluation of liver cirrhosis and portal hypertension. Dis Markers 2011;31:129–38.
30. Gastrointestinal Expert Group. Advanced liver disease: Ascites. In: eTG Complete [Internet]. Melbourne:Therapeutic Guidelines Ltd, 2013. Available at www.tg.org.au [Accessed 14 April 2014].
31. Liou IW. Management of end-stage liver disease. Med Clin North Am 2014;98:119–52.
32. García-Pagán JC, Gracia-Sancho J, Bosch J. Functional aspects on the pathophysiology of portal hypertension in cirrhosis. J Hepatol 2012;57:458–61.
33. Kuiper JJ, van Burren HR, de Man RA. Ascites in cirrhosis: a review of management and complications. Neth J Med 2007;65:283–88.

CASE 4

SHIRLEY ASKS FOR REPEAT SCRIPTS

Shirley Smith, aged 75 years, has just moved to a local retirement village and comes to your practice for the first time. She presents 'just for repeat scripts'. Her medical history includes stable, medically treated ischaemic heart disease, hyperlipidaemia, depression and severe osteoarthritis affecting her back, hips and knees.

Her current medications are rosuvastatin 5 mg, isosorbide mononitrate 60 mg, aspirin 100 mg and meloxicam 15 mg, each daily, and sertraline 50 mg at night. She also takes paracetamol 500–1000 mg as neeeded. She is a non-smoker and rarely drinks alcohol.

QUESTION 1

What is your initial assessment of Shirley's situation?

FURTHER INFORMATION

On specific questioning, Shirley says she has had some mild indigestion, nausea and anorexia intermittently over the last few weeks. She has not noticed any weight loss. She has not had much indigestion before. Her bowel motions are normal. Shirley says that her other doctor advised her to stop taking meloxicam but she 'couldn't move' without it. Her previous doctor had also recommended exercise but she hates aqua aerobics. Examination reveals reduced mobility due to low back pain. Abdominal examination is normal. Her weight is 55 kg and BMI 23 kg/m^2.

QUESTION 2

Does Shirley need investigation(s)? If so, what will you arrange initially?

FURTHER INFORMATION

Full blood examination is normal. Biochemistry shows normal renal function and liver chemistry, which are unchanged from past results. Gastroscopy reveals mild erosive antral gastritis but no ulcer. Gastric biopsies show active chronic gastritis but no intestinal metaplasia. *H. pylori* is present.

QUESTION 3

What should happen next?

FURTHER INFORMATION

After determining that Shirley is not allergic to penicillin, you treat her with triple therapy comprising esomeprazole, amoxicillin and clarithromycin for 1 week, in accordance with current recommendations[1] for first-line *H. pylori* eradication therapy. She is apparently compliant but when a breath test is done some weeks later, the the infection is still present.

QUESTION 4

What do you do now?

FURTHER INFORMATION

Shirley was referred to a specialist and was given second-line *H. pylori* eradication therapy. When re-tested some weeks later, the breath test was negative. Her symptoms had diminished but were not abolished.

QUESTION 5

Is Shirley now adequately protected if she needs ongoing NSAID therapy? What changes to her management would you recommend now?

CASE 4 ANSWERS

ANSWER 1

Her current medications put her at a very high risk of peptic ulceration and bleeding in addition to the cardiovascular and renal risks of her non-steroidal anti-inflammatory drug (NSAID). All NSAIDs confer some risk of peptic ulceration (odds ratio [OR] up to 18) and gastrointestinal bleeding (OR up to 5).[2] Meloxicam, although often considered a COX-2-selective agent, is more a traditional non-selective NSAID. It is at the mid-to-high end of the risk spectrum, compared with some other NSAIDS, and the higher dose that Shirley is using further increases risk.[3] In any case, her use of low-dose aspirin would abolish any gastrointestinal-protective effect of COX-2-selective NSAIDs.[3,4] Aspirin confers a modest independent risk of gastrointestinal bleeding, additive with her NSAID risk.[5]

Selective serotonin reuptake inhibitors (SSRIs) increase the risk of gastrointestinal bleeding[6] independently of (OR 2.36) and synergistically with NSAIDs (OR 6.3).[7] The increased bleeding may be due to reduced serotonin uptake by the platelets leading to impaired platelet function and aggregation.[7] Enquiry should be made as to whether she is also using over-the-counter NSAIDs.

Lastly, it would be important to re-assess the indication for low-dose aspirin. A cardiovascular opinion could be sought if there was any doubt about the suitability of ceasing aspirin for Shirley.[4]

ANSWER 2

Shirley's symptoms need investigation given her age, medications and new-onset gastrointestinal symptoms. Upper abdominal pain or discomfort has been reported in up to 50% of people who use NSAIDs but symptom assessment cannot distinguish between NSAID-related dyspepsia and pain due to peptic ulceration. Up to 30% of people who use NSAIDs have ulcers at endoscopy. Many of these people are asymptomatic until complications occur.[1,8]

Blood tests that should be done include full blood examination, iron studies to exclude anaemia and biochemistry for renal function, liver chemistry and lipids. As she is elderly, has new upper gastrointestinal symptoms and is at high risk, she should be referred for gastroscopy. Her past medical file should be obtained for details of past investigations and management of her arthritis and comorbidities.

ANSWER 3

Shirley should have eradication therapy for *H. pylori*. This infection independently increases the risk of ulceration and bleeding and the risk is synergistic with NSAID use.[2] There is a 60-fold increase in the risk of peptic ulcer detected by endoscopy in those who are infected and take NSAIDs; the risk of bleeding is increased more than 6-fold, compared with those without either risk factor.[2] Moreover, the risk of complications (bleeding and perforation) is very much higher in the elderly, particularly those aged ≥75 years and those with comorbidities.[8]

Evidenced-based clinical guidelines recommend testing for and treating *H. pylori* in at-risk patients taking NSAIDs even in the absence of symptoms, as eradication has been shown to reduce the risk of ulceration and bleeding.[1,9,10] Presentation to hospital with complications is frequently the first manifestation of ulcer disease, especially in the elderly.

Despite the evidence of benefit, surveys show that *H. pylori* testing and treatment are often overlooked in this context.

Testing for the outcome of eradication therapy is required, usually with a urea breath test done more than 4 weeks after the end of therapy.[1] To minimise the chances of a false-negative result, antibiotics and bismuth should not be taken for a at least 1 month and proton pump inhibitors (PPIs) should be ceased for at least 1 week (preferably 2 weeks) before breath testing. Histamine H_2-receptor antagonist treatment may be continued as it does not interfere with testing.[1]

ANSWER 4

Eradication of *H. pylori* remains highly desirable as a risk-reduction strategy. Failure of first-line therapy is not uncommon in general practice. Clinical trials report success rates of 85–90% for first-line eradication; however, lower rates are achieved in practice.[11] Unfortunately, repeating the same triple therapy is a poor strategy as secondary clarithromycin resistance usually occurs after failed therapy and the likelihood of treatment success with the same therapy is slim (<10%).[1,9,10] This creates a dilemma for GPs as there is only one combination *H. pylori* triple therapy registered in Australia. In practice, some GPs repeat first-line therapy and others try ad hoc combinations that are either not evidenced-based or have been shown to be ineffective; such attempts are usually unsuccessful.

There are a number of proven second-line therapies to treat first-line eradication failures but these combinations require approval through the Special Access Scheme, as components of these therapies are not registered in Australia and often have to be brought in from abroad. Unless a GP has particular expertise in this area, patients with difficult-to-eradicate *H. pylori* should be referred for expert advice. These therapies are outlined in the current edition of *Therapeutic Guidelines: Gastrointestinal*[1] and elsewhere.[9,10]

ANSWER 5

Although eradication of *H. pylori* reduces her risk of gastrointestinal problems, Shirley remains at a significant ongoing risk of ulceration and gastrointestinal bleeding as she is elderly, has comorbidities and is taking an NSAID and an SSRI (her aspirin was ceased). She has ongoing NSAID-related cardiovascular risks also.

Her arthritis and pain management need revision. The next steps are to determine if she can do without regular NSAID therapy by substituting regular analgesics (rather than prn), typically paracetamol. Note that this strategy reduces the risks of ulceration and bleeding but, anecdotally, may be associated with liver toxicity, particularly in a low-weight older patient. However, a recent review suggests that the risk of hepatotoxicity from therapeutic doses of paracetamol is extremely low.[12] Non-drug physical therapies or other therapies to treat her pain and reduced mobility should be fully explored.

If Shirley cannot manage without NSAID therapy, an agent that balances gastrointestinal and cardiovascular risk is required. At present, naproxen has been associated with the lowest cardiovascular risk profile and, given her history of ischaemic heart disease, is preferred over a COX-2-selective agent, even though the latter have a somewhat lower risk of adverse gastrointestinal effects.[13] Naproxen is considered mid-range for gastrointestinal risk.[3] The lowest necessary dose should be used with review as to whether it is needed regularly or intermittently.

Her need for an SSRI should be reviewed, as it is an independent risk factor for bleeding, as discussed earlier, and should be ceased if possible.

Lastly, given Shirley's multiple ongoing risk factors for peptic ulcer disease and bleeding, a standard dose of a PPI once daily should be prescribed as prophylaxis if NSAIDs are continued. The evidence shows that such primary prophylaxis reduces ulceration in patients treated with either non-selective or COX-2–selective NSAIDs, and it is recommended for patients at higher risk.[14–16] Treatment with PPIs can be ceased if NSAIDs are no longer required.

REFERENCES

1. Expert Group for Gastrointestinal. Gastric disorders. Therapeutic Guidelines. In: eTG Complete [Internet]. Melbourne: Therapeutic Guidelines Ltd, 2013. Available at www.tg.org.au [Accessed 24 March 2014].
2. Huang JQ, Sridhar S, Hunt RH. Role of *Helicobacter pylori* infection and non-steroidal anti-inflammatory drugs in peptic-ulcer disease: a meta-analysis. Lancet 2002;359:14–22.
3. Castellsague J, Riera-Guardia N, Calingaert B, et al. Safety of non-steroidal anti-inflammatory drugs (SOS) project. Individual NSAIDs and upper gastrointestinal complications: a systematic review and meta-analysis of observational studies (the SOS project). Drug Safety 2012;35:1127–46.
4. National Vascular Disease Prevention Alliance. Absolute cardiovascular disease management. Quick reference guide for health professionals, 2012. National Stroke Foundation. Available at http://strokefoundation.com.au/site/media/NVDPA-Managment-Guideline-Quick-Reference-Guide.pdf [Accessed online 24 March 2014].
5. Sørensen HT, Mellemkjaer L, Blot WJ, et al. Risk of upper gastrointestinal bleeding associated with use of low-dose aspirin. Am J Gastroenterol 2000;95:2218–24.
6. Expert Group for Psychotropic. Management of antidepressant adverse effects. In: eTG Complete [Internet]. Melbourne:Therapeutic Guidelines Ltd, 2013. Available at www.tg.org.au [Accessed 24 March 2014].
7. Loke YK, Trivedi AN, Singh S. Meta-analysis: gastrointestinal bleeding due to interaction between selective serotonin uptake inhibitors and non-steroidal anti-inflammatory drugs. Aliment Pharmacol Ther 2008;27:31–40.
8. Gutthann SP, García Rodríguez LA, Raiford DS. Individual nonsteroidal antiinflammatory drugs and other risk factors for upper gastrointestinal bleeding and perforation. Epidemiology 1997;8:18–24.
9. Fock KM, Katelaris P, Sugano K, et al. Second Asia-Pacific Consensus Guidelines for *Helicobacter pylori* infection. J Gastroenterol Hepatol 2009;24:1587–600.
10. Malfertheiner P, Megraud F, O'Morain CA, et al. European Helicobacter Study Group. Management of *Helicobacter pylori* infection – the Maastricht IV/Florence Consensus Report. Gut 2012;61:646–64.

11. Antibiotics Expert Group. Antibiotics: eradication of *Helicobacter pylori* and ulcer healing. In: eTG Complete [Internet]. Melbourne: Therapeutic Guidelines Ltd, 2013. Available at www.tg.org.au [Accessed 3 March 2014].
12. Graham GG, Davies MJ, Day RO, Mohamudally A. Scott KF. The modern pharmacology of paracetamol: therapeutic actions, mechanism of action, metabolism, toxicity and recent pharmacological findings. Inflammopharmacol 2013;21:201–32.
13. Coxib and traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet 2013;382:769–79.
14. Scheiman JM, Yeomans ND, Talley NJ, et al. Prevention of ulcers by esomeprazole in at-risk patients using non-selective NSAIDs and COX-2 inhibitors. Am J Gastroenterol 2006;101:701–10.
15. Rostom A, Muir K, Dube C, Lanas A, Jolicoeur E, Tugwell P. Prevention of NSAID-related upper gastrointestinal toxicity: a meta-analysis of traditional NSAIDs with gastroprotection and COX-2 inhibitors. Drug Health Patient Saf 2009;1:47–71.
16. Rostom A, Moayyedi P, Hunt R; Canadian Association of Gastroenterology Consensus Group. Canadian consensus guidelines on long-term non-steroidal anti-inflammatory drug therapy and the need for gastroprotection: benefits versus risks. Aliment Pharmacol Ther 2009;29:481–96.

CASE 5

KEN IS REJECTED BY THE BLOOD BANK

Ken, an electrician aged 35 years, lives with his wife and two sons aged 12 and 10 years. He was a regular plasma donor for many years, but stopped several years ago because of time pressures at work. He decides to resume donating blood after hearing about the shortage of plasma donations at the blood bank. Before his donation, the blood bank informs him that his blood count (from a skin prick test) is at the lower limit of normal.

A few days after the donation, he receives a follow-up letter from the blood bank informing him that his ferritin levels are low and that a blood film showed hypochromic microcytic changes. The letter advises him to see his GP and informs him that he cannot make further blood donations at the present time. He is annoyed about this and comes to see you, his wife's GP. He hasn't seen a GP for 10 years, is not vegetarian and says he is otherwise well.

When asked about other symptoms, he admits to feeling a bit tired. He has also been having mild intermittent flatulence, bloating and loose stools for many years. He has always attributed his bowel symptoms to irritable bowel syndrome (IBS) because his mother has the same problem. Ken's weight has been stable for many years.

Ken's physical examination is normal. His BMI is 20 kg/m^2.

QUESTION 1

What is the most likely diagnosis?

QUESTION 2

What specific investigations will you order for Ken to make the diagnosis you think is most likely?

QUESTION 3

What are common presenting symptoms of coeliac disease?

FURTHER INFORMATION

Ken undergoes all of the investigations you recommended and returns for the results. The tests confirm the diagnosis you thought was most likely.

QUESTION 4

How would you explain Ken's condition to him using lay terms?

QUESTION 5

Outline your management of Ken's condition using the following subheadings: initial, ongoing monitoring, follow-up and annual review.

QUESTION 6

Who in Ken's family should be offered screening?

CASE 5 ANSWERS

ANSWER 1

The most likely diagnosis is coeliac disease as Ken has a range of symptoms commonly associated with this condition.[1,2] Differential diagnoses include IBS with another cause of iron deficiency anaemia, non-coeliac gluten intolerance with another cause of iron deficiency anaemia, inflammatory bowel disease, diverticular disease and bowel cancer (unlikely).[1]

Coeliac disease is a common, yet underdiagnosed condition that has a broad spectrum of presentations. Diagnosing coeliac disease, therefore, requires a high level of suspicion. It affects at least one in 100 Australians;[3,4] however, about three in four patients remain undiagnosed.[3] The age of onset ranges from 6 months to >90 years.[2]

ANSWER 2

Investigations to diagnose coeliac disease include serological testing for coeliac-specific antibodies and duodenal mucosal biopsy confirmation.[1,3] The most sensitive and specific blood tests for coeliac disease are tissue transglutaminase antibody (tTG) and deamidated gliaden peptide (DGP) antibody.[1,2] It is also important to order a total immunoglobulin A (IgA) level[1] because 2–5% of patients with coeliac disease have IgA deficiency, which makes their coeliac antibody tests unreliable.[3]

Patients must be consuming sufficient gluten (equivalent of four slices of bread per day for 6 weeks) for coeliac serology and small bowel biopsy to be accurate diagnostic investigations.[1,2,5] If a patient is already on a gluten-free diet and refuses to re-introduce gluten into the diet because they feel so much better without it, genetic testing for HLA DQ8 and HLA DQ2, performed by taking a buccal smear or blood sample, may help. However, the result is only useful if it is negative (99.6% of patients with coeliac disease have one of HLA DQ8 or HLA DQ2, but so do one-third of the general Australian population[3]). In other words, the genetic test is one of exclusion only. Only one in 30 people with these genes develop coeliac disease.[3,6] In Ken's case, it is also appropriate to order a full blood examination, iron studies and assess vitamin B12, folate levels and vitamin D.[2]

The gold standard for the diagnosis of coeliac disease is currently a small bowel biopsy.[1,2] However, more sensitive and specific blood tests may be available in future. The key finding on small biopsy is villous atrophy. Small bowel damage is usually patchy, so four samples, taken from different points of the duodenum, are required to ensure the result is not a false negative.[3]

If there is a strong clinical suspicion of coeliac disease and serology is negative, a small bowel biopsy should still be considered.[2]

ANSWER 3

Common symptoms of coeliac disease may include:

- IBS-type symptoms:[1,2,5]
  - bloating, flatulence and a variation in bowel habit (eg loose

stools/diarrhoea or constipation, or a combination of both)
  - abdominal pain and/or discomfort
- nausea[3]
- fatigue[3]
- iron deficiency anaemia[3] (eg discovered by the blood bank)
- nutritional deficiencies[3] (eg iron and folate, zinc, vitamin B12 and vitamin D)
- failure to thrive in children.[3]

Less common but important presentations include:

- osteoporosis – onset may be early due to a lack of absorption of calcium and vitamin D[5]
- infertility[3]
- recurrent miscarriage[5]
- mood disorders (eg depression, bipolar)[5]
- recurrent mouth ulcers[5]
- polyneuropathy/peripheral neuropathy[5]
- cerebellar ataxia[3]
- dermatitis herpetiformis[7]
- abnormal liver function tests.[5]

ANSWER 4

The following text is an example of how you might explain the diagnosis to Ken.

'Ken, coeliac disease is a condition in which the body reacts to gluten, a protein found in wheat, barley, rye and oats. The reaction causes damage to the small bowel. If you look at a part of the small bowel under a microscope, it has tiny fingers called villi that line the bowel. They have an important role in absorbing nutrients from the food we eat after being broken down. In coeliac disease, the villi are flat and inflamed, so you are not absorbing the required nutrients from your food. This has caused you to be low in iron and possibly other nutrients, which we need to test you for.'

You could use a diagram and/or your fingers to illustrate this.

ANSWER 5

Initial management[2,3,6]

Ideally, this should involve the person in the family who does most of the cooking and shopping, in this case, Ken's wife. The cornerstone management of coeliac disease is a lifelong gluten-free diet. This allows the damaged villi to recover and grow back, leading to an improvement in symptoms. It also prevents long-term complications, such as bowel lymphoma, osteoporosis, infertility and chronic ill-health in symptomatic or asymptomatic patients with coeliac disease. For a person with coeliac disease who maintains a gluten-free diet, the risk of these complications is no greater than that for people without coeliac disease.

Ken should be advised to join the Coeliac Society in his state or territory (www.coeliac.org.au or phone 1300 GLUTEN) as soon as possible. He also needs a doctor's letter confirming his diagnosis for the Coeliac Society.

The Coeliac Society offers various resources, including a list of gluten-free foods and coeliac-friendly restaurants, recipes and gluten-free products, an ingredient book that indicates whether or not something is gluten-free, dietitians with a special interest in coeliac disease, support groups, a magazine with updates on research, supermarket tours that explain how to read food labels and tips for travelling.

Additional initial management steps for Ken include:

- Commencement of a gluten-free diet, starting with 1) naturally occurring gluten-free foods (eg fruit, vegetables, eggs and meat), and 2) products labelled 'gluten-free'. Further information is available from the Gastroenterological Society of Australia (GESA) website[2] and the Coeliac Society.[6] It is essential that patients and their partners/carers learn how to read food labels accurately so they can avoid the accidental ingestion of gluten, which may be present in less obvious sources such as sausages, processed meats, soups, ice creams, sauces, dressings and stock cubes.
- Identify gluten-free foods using, for example, the ingredients list booklet (available for members from the Coeliac Society) or the Coeliac Society of Australia's smartphone app that identifies gluten-free products not marked as such but contain only gluten-free ingredients.
- Diagnose and treat any nutritional deficiencies (eg iron, vitamin B12, folate, calcium, phosphate, magnesium, zinc and vitamin D).
- Educate Ken to check that all of his medications are gluten-free. These medications include all over-the-counter medicines, vitamins and herbal preparations. He may need to ask his doctor or pharmacist to check if a product is gluten-free. Useful resources for this include MIMS or Consumer Medical Information (www.nps.org.au or phone 1300 633 424).
- Screen Ken for the more common conditions associated with coeliac disease. These include type 1 diabetes mellitus, hypothyroidism, thyrotoxicosis, glomerulonephritis and pernicious anaemia. Investigations for these conditions include renal function tests (urea, electrolytes and creatinine), liver function tests, thyroid function tests and fasting blood glucose.[5]
- Perform a bone mineral density test (DEXA) of the hips and spine. All adults with coeliac disease should have a DEXA scan to screen for osteoporosis or osteopenia at the time of diagnosis.[2] People with medically diagnosed coeliac disease are able to claim the Medicare rebate for a DEXA scan done every 2 years if required (one in three adults with newly diagnosed coeliac disease has decreased bone density).
- Refer Ken to a dietitian, preferably one who specialises in coeliac disease (contact the Coeliac Society or the Dieticians Association of Australia for a list). Patients tend to gain weight after their villi regenerate as they absorb more nutrients.
- Assess and monitor Ken's mental state. Emotional reactions to the diagnosis of coeliac disease can vary from relief to shock, despair, grief, disbelief, guilt for passing it on to one's children, or a feeling of being overwhelmed.

- Provide supportive counselling and/or refer Ken to a psychologist if needed.
- Consider preparing a care plan for Ken.

Ongoing monitoring and follow-up after initial diagnosis[2,3,6]

People with coeliac disease require regular monitoring and follow-up, focusing on nutritional deficiencies and dietary compliance. Gluten can sometimes be ingested unintentionally, and this is the most common cause of persistently elevated coeliac serology tests.

At 6 months repeat coeliac serology (tTG DGP and total IgA) and other relevant blood tests, depending on abnormalities at diagnosis (eg low nutrients).

At 12 months repeat relevant tests (ie full blood examination [FBE], iron studies, vitamin B12, folate, calcium, phosphate, magnesium, zinc, vitamin D, thyroid function tests [TFTs], liver function tests [LFTs], urea, electrolytes creatinine [UEC], fasting blood glucose and coeliac serology) to monitor long-term progress and adherence to the gluten-free diet.

At 12–24 months repeat duodenal biopsy to review the histology of villi.[6] Some debate exists as to whether this should be standard practice for patients who are responding well to a gluten-free diet.[3]

Annual review[2]

Coeliac serology and repeat blood tests should be ordered on a 12-monthly basis to assess dietary compliance, nutritional deficiencies and possible complications. Follow-up with a referral to a dietitian if needed.

ANSWER 6

All first-degree relatives of a patient with confirmed coeliac disease should be advised to have screening using coeliac serology.[1] In Ken's case, first-degree relatives are his parents, any siblings and his children. It is particularly important to screen his mother if she has never been screened, given she has been told she has IBS. The risk of coeliac disease in an individual who has a family member with this condition is 10%.[3,6,8] The identical twin of a patient with coeliac disease has a 70% chance of developing coeliac disease, indicating a multifactorial aetiology for coeliac disease.[6]

REFERENCES

1. Rubio-Tapia A, Hill, ID, Kelly CP, Calderwood AH, Murray JA. ACG clinical guidelines: diagnosis and management of celiac disease. Am J Gastro 2013;108:656–76.
2. Gastroenterological Society of Australia. Coeliac Disease: clinical update. Sydney: Digestive Health Foundation, 2007. Available at www.gesa.org.au/files/editor_upload/File/Professional/Coeliac_Disease4Ed07.pdf [Accessed 24 March 2014].
3. Ellard K, Shepherd, S. Coeliac disease. How to Treat. Australian Doctor 2012;pp 31–8.
4. Anderson RP, Henry MJ, Taylor R, et al, A novel serogenetic approach determines the community prevalence of celiac disease and informs improved diagnostic pathways. BMC Med 2013;11:188–203.
5. National Institute for Health and Clinical Excellence. Coeliac disease: recognition and assessment of coeliac disease. Quick reference guide. NICE clinical guideline 86, issued May 2009. Available at www.nice.org.uk/nicemedia/live/12166/44355/44355.pdf [Accessed 5 March 2014].
6. Coeliac Society of Australia. Available at www.coeliacsociety.com.au/coeliac-disease (Accessed 4 March 2014).
7. Welsh, B. Blistering skin conditions. Aust Fam Physician 2009;38:484–90.
8. Rubio-Tapia A, van Dyke CT, Lahr BD, et al. Predictors of family risk for celiac disease: a population-based study. Clin Gastroenterol Hepatol 2008;6:983–87.

RESOURCES FOR PATIENTS AND DOCTORS

- Coeliac Australia has a number of useful resources. www.coeliac.org.au/resources/
- Gastroenterological Society of Australia. www.gesa.org.au/consumer.asp?id=45

RESOURCES FOR DOCTORS

- Welsh, B. Blistering skin conditions. Aust Fam Physician 2009;38:484–90. This article contains information about the features and management of dermatitis herpetiformis, a rare but important presentation of coeliac disease.
- Gibson P. Irritable bowel syndrome. How to Treat. Australian Doctor 13 April 2012:27–34 (includes fructose malabsorption).

Gastroenterology

In order to qualify for 6 Category 2 points for the QI&CPD activity associated with this unit:

- read and complete the unit of *check* in hard copy or online at the *gplearning* website at http://gplearning.racgp.org.au
- log into the *gplearning* website at http://gplearning.racgp.org.au and answer the following 10 multiple choice questions (MCQs) online
- complete the online evaluation.

If you are not an RACGP member, please contact the *gplearning* helpdesk on 1800 284 789 to register in the first instance. You will be provided with a username and password that will enable you access to the test.

The expected time to complete this activity is 3 hours.

Do not send answers to the MCQs into the *check* office. This activity can only be completed online at http://gplearning.racgp.org.au

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

FOR A FULL LIST OF ABBREVIATIONS AND ACRONYMS USED IN THESE QUESTIONS PLEASE GO TO PAGE 3.
FOR EACH QUESTION BELOW SELECT ONE OPTION ONLY.

QUESTION 1

Which statement about coeliac disease is CORRECT?

A. Coeliac disease affects at least one in 1000 Australians, the age of onset ranges from 6 months to ≥90 years and the risk of coeliac disease in an individual with an affected family member is around 70%.

B. Coeliac disease affects at least one in 10,000 Australians, the age of onset ranges from 6 months ≥90 years and the risk of coeliac disease in an individual with an affected family member is around 10%.

C. Coeliac disease affects at least one in 100 Australians, the age of onset ranges from 6 months to ≥90 years and the risk of coeliac disease in an individual with an affected family member is around 70%.

D. Coeliac disease affects at least one in 1000 Australians, the age of onset ranges from 6 months to middle age (40–50 years) and the risk of coeliac disease in an individual with an affected family member is around 10%.

E. Coeliac disease affects at least one in 100 Australians, the age of onset ranges from 6 months to ≥90 years and the risk of coeliac disease in an individual with an affected family member is around 10%.

QUESTION 2

Jade, aged 18 years, and her boy friend Flyn, aged 19 years, are planning to take a gap year and travel around the world. They plan to visit a number of regions and countries, including South East Asia, the United States of America, Brazil (for the soccer World Cup), England, France, Spain and Portugal, as well as Germany to visit Jade's relatives. Initially, they will spend 2 months travelling through South East Asia. They have come to see you for a pre-travel consultation under advice from Jade's mother who is a registered nurse. Which of the following is CORRECT?

A. Any travel medicine advice provided to them should take into account their destinations, duration of travel, time of year, activities to be undertaken and their personal health.

B. It will be important to ensure that Jade and Flyn receive appropriate vaccinations, given the diversity of the regions/countries that they are travelling to.

C. Jade and Flyn should be provided with detailed information on preventative measures and be given detailed printed information on problems they might encounter (eg traveller's diarrhoea) as well as medications for the treatment of diarrhoea.

D. Answers A, B and C are correct.

E. Answers A and B are correct.

QUESTION 3

David is a retired lawyer, aged 67 years, who presents complaining of burning pain in his abdomen, nausea and indigestion-like symptoms that he believes have crept up on him over a period of months. He has hypertension, which was diagnosed 3 years ago and for which he takes ramipril 10 mg daily. In recent years he has been taking paracetamol and ibuprofen for joint pain. David claims the pain was pretty bad this winter and he was using a lot more painkillers than usual. He used to take low-dose aspirin until recently, when a GP in your practice advised him to stop taking it. He was treated for *Helicobacter pylori* infection last year. On questioning, he thinks his current gastric symptoms are mild, compared with his symptoms prior to diagnosis of *H. pylori* infection. Which of the following statements is the most CORRECT?

A. David's symptoms are due to his use of ibuprofen or some other gastric problem, not *H. pylori* infection.

B. David should have baseline blood investigations and *H. pylori* testing and, depending on the outcomes of these investigations, might need a referral for gastroscopy; he could also benefit from referral to a rheumatologist to assess his joint pain.

C. David should be asked to cease use of his ibuprofen and see you again in 2 weeks for a review.

D. On the basis of David's history and presenting symptoms, he should be tested for *H. pylori* infection, treated, if positive, and referred to a rheumatologist to get assess his joint pain.

E. On the basis of David's history and presenting symptoms, he should be prescribed a proton pump inhibitor and referred to a rheumatologist to assess his joint pain.

QUESTION 4

Which of the following statements regarding NAFLD/NASH is CORRECT?

A. By definition, NAFLD is a condition that involves hepatic steatosis on imaging or by histology and occurs in patients with little or no history of alcohol consumption.

B. NASH may progress to cirrhosis in up to 80% of patients.

C. The prevalence of NAFLD has tripled in last the 20 years and its major risk factors (eg central obesity, type 2 diabetes mellitus, dyslipidaemia, and metabolic syndrome) are increasingly prevalent.

D. Screening for NAFLD in high-risk groups is recommended and this could be incorporated into the health assessment for people aged 45–49 years who are at risk of developing chronic disease.

E. Evidence-based drug therapy for NASH includes the use of diabetes drugs targeting insulin resistance.

QUESTION 5

Which of the following statements regarding alcoholic liver disease is CORRECT?

A. In the case of suspected alcoholism or alcohol-related conditions, it is not necessary to obtain a patient's permission to interview family members to help determine the patient's alcohol consumption.

B. Patients with alcoholic fatty liver who are not malnourished on presentation do not require nutritional assessment.

C. In patients with alcoholic liver disease who have not progressed to cirrhosis, abstinence may allow for reversal of the hepatic changes induced by alcohol.

D. Alcoholic cirrhosis represents an early stage of progressive hepatic fibrosis and liver damage in those with alcoholic liver disease.

E. People with alcoholic liver disease and ascites do not need to restrict their use of dietary sodium.

QUESTION 6

Judy is a pianist, aged 29 years, and has a long history of irritable bowel type symptoms and anaemia. She has recently been diagnosed with coeliac disease. She presents with her partner to discuss her results and management. Which of the following statements outlines the BEST management plan for Judy?

A. Judy needs to be educated about coeliac disease.

B. Judy needs to be educated about coeliac disease and her first-degree relatives should be screened for the condition.

C. Judy's first-degree relatives need to be encouraged to be screened for the condition.

D. Judy needs to be educated about coeliac disease and its management (eg gluten-free diet, screening for associated conditions, regular review and screening of first-degree relatives).

E. Judy needs to commence a gluten-free diet immediately and be assessed for nutritional deficiencies, which if identified, should be treated.

QUESTION 7

Which of the following statements is CORRECT with regards to travel to India?

A. The risks of food-borne and water infections are potentially high in India and prevention strategies, including vaccinations, should be discussed and encouraged as a minimum.

B. For people travelling to India, antibiotic prophylaxis is not (routinely) recommended to prevent traveller's diarrhoea; however, where treatment is required, current antimicrobial resistance patterns support the use of azithromycin as a first-line antibiotic, at a dose of 500 mg twice daily for 3 days.

C. For people travelling to India, antibiotic prophylaxis is not (routinely) recommended to prevent traveller's diarrhoea; however, patients should be provided with information on traveller's diarrhoea and medications, should a problem arise.

D. Answers A, B and C are correct.

E. Answers A and C are correct.

QUESTION 8

Which of the following statements is CORRECT regarding gastric ulcers?

A. Up to 70% of people using NSAIDs are likely to have an ulcer on endoscopy but not all of these people are likely to be symptomatic.

B. Not all NSAIDs are associated with gastric ulcers and gut bleeding.

C. The potential benefits of prescribing a COX-2-selective NSAID are abolished when a person uses aspirin concurrently with the COX-2-selective NSAID.

D. H. pylori infection independently increases the risk of a gastric ulcer and gastric bleeding but concurrent use of NSAIDs attenuates this risk.

E. If testing shows that first-line *H. pylori* eradication has failed, triple therapy should be repeated.

QUESTION 9

Serena is a widow aged 57 years. She presents requesting repeat prescriptions for her blood pressure medications. She complains of tiredness and a nagging persistent pain in the upper right part of her abdomen. On examination her liver feels slightly enlarged. Her blood pressure is 151/81 mmHg today and her BMI is 33.6 kg/m^2. Since her husband's death a few years ago, Serena has gained weight and has gone up two dress sizes. She rarely drinks, perhaps consuming half a glass of champagne once or twice a year at a wedding or a christening. Which of the following statements is the most CORRECT?

A. Serena should have blood samples taken for investigation of her liver function and she may require additional investigations such as an ultrasound or biopsy, depending on the findings.

B. Given her presenting history, Serena may have NAFLD as most patients are asymptomatic and the symptoms she reports often occur in NAFLD.

C. If Serena is diagnosed with NAFLD/NASH she would need to be advised to lose weight and make other lifestyle modifications to slow progression.

D. Differential diagnosis for her presenting symptoms may need to include testing for hepatitis A, B and C.

E. All of the above are true.

QUESTION 10

Andrew, 45 years of age, is a divorced war veteran who suffered from post-traumatic stress disorder after the Afghanistan war and had major depression. He also has a longstanding drinking problem and alcoholic liver disease. He takes medication for his depression and uses paracetamol and a prescribed NSAID regularly to manage pain from a war injury. He takes a herbal product that his mother bought for him to help him sleep. His regular GP is on leave and he has come to see you to discuss the results of his recent liver ultrasound, which shows a cirrhotic liver. Which of the following statements is CORRECT?

A. Portal hypertension is a major complication of cirrhosis and it has been implicated in the development of ascites; however, ascites itself is a benign condition.

B. Patients with cirrhosis are at increased risk of medication adverse events because of impaired hepatic metabolism and some medications may require dose adjustments, while others should be avoided.

C. Patients with cirrhosis should not receive vaccinations.

D. While portal hypertension is a major complication of cirrhosis it has not been implicated in the development of ascites.

E. A diagnosis of ascites can be made on the basis of examination alone.

check

Independent learning program for GPs

check

Independent learning program for GPs

Unit 506 June 2014

Fatigue

RACGP

www.racgp.org.au/check

Subscriptions

For subscriptions and enquiries please call 1800 331 626 or email check@racgp.org.au

Published by

The Royal Australian College of General Practitioners
100 Wellington Parade
East Melbourne, Victoria 3002, Australia
Telephone 03 8699 0414
Facsimile 03 8699 0400
www.racgp.org.au

ABN 34 000 223 807
ISSN 0812-9630

check

Independent learning program for GPs

Fatigue

Unit 506 June 2014

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

ABOUT THIS ACTIVITY

Tiredness or fatigue is a common presentation in general practice. Although a normal part of life, ongoing (chronic) fatigue may be a symptom of a serious undiagnosed illness. Infectious disease, anaemia, undiagnosed endocrine problems, sleep problems, side effects of medication and malignancies may be causes of fatigue.[1] On average, however, investigations have a low rate of identifying underlying disease.[2] The management approach to patients presenting with fatigue is to rule out common organic diseases without over-investigating.[1]

This edition of *check* considers fatigue scenarios of relevance to general practice in Australia, focusing on common causes of fatigue.

LEARNING OUTCOMES

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

- outline management options for patients diagnosed with hypothyroidism
- describe investigations used to diagnose iron deficiency anemia and discuss results that require further investigation
- summarise the diagnosis and management of myasthenia gravis
- describe the diagnosis and management of chronic fatigue syndrome/myalgic encephalitis
- list considerations when developing a management plan for a person diagnosed with fibromyalgia.

AUTHORS

Katie Ellard MBBS, FRACP is a gastroenterologist in private practice at St Leonards in Sydney. Her particular interests are inflammatory bowel disease, functional gut disease and quality assurance in colonoscopy. She is the secretary of the Gastroenterological Society of Australia.

Emma Guymer MBBS, FRACP is a rheumatologist with a professional interest in general rheumatology and fibromyalgia. She is head of the Fibromyalgia Clinic at Monash Medical Centre in Clayton, Melbourne.

Donald McLeod BSc, MBBS (Hon), FRACP, MPH is an endocrinologist and general physician at the Royal Brisbane & Women's Hospital. After completing his clinical training, Don undertook a Masters of Public Health at Harvard School of Public Health, and a research fellowship in thyroid cancer at The Johns Hopkins University School of Medicine, both in the USA. He is completing his PhD in epidemiology at QIMR Berghofer Medical Research Institute. His clinical interests encompass all thyroid disease, and his research focuses on the causes of thyroid cancer and thyroid autoimmunity.

Pei Xuan Ong MBBS (Hon) is a rheumatology advanced trainee at Monash Health. She has a special interest in systemic lupus erythematosus and fibromyalgia.

John Scally MBBS DObst, RCOG, FRACGP, CTH was an examiner for the RACGP and contributor to *Therapeutic Guidelines–Gastrointestinal*. He has been in general practice for 40 years and has a special interest in travel medicine.

Sara Whitburn BMBS, FRACGP is a general practitioner and family planning doctor working in Melbourne, Victoria. She has a special interest in women's health and children's health, particularly early childhood.

PEER REVIEWERS

Linda Barrett MBBS, FRACGP has worked as a general practitioner in Sydney, and as a medical educator and examiner for the RACGP. She has developed, reviewed and presented educational content for the RACGP.

Carol Lawson MBBS, Dip Obst, MFM (Monash), FRACGP is currently a general practitioner in Brunswick, Melbourne, and a QA examiner with the RACGP. She spent 10 years as an academic GP with the Department of General Practice at Monash University, and has special interests in medical education and women's health.

Kathryn Robinson MBBS FRACP FRCPA is a haematologist and transfusion medicine specialist at the Australian Red Cross Blood Service and the Queen Elizabeth Hospital in Adelaide, South Australia. Kathryn is the clinical lead of BloodSafe, a statewide collaborative program to improve the safety and appropriateness of clinical transfusion practice. She has a particular interest in iron deficiency and has been involved in a number of improvement programs, including the development of resources and academic detailing programs for general practitioners. Kathryn was involved in the development of the National Patient Blood Management Guidelines (medical module) as member of the expert working group.

REFERENCES

1. Ponka D, Kirlew M. Top 10 differential diagnoses in family medicine: Fatigue. Cand Fam Physcian 2007;53:892.
2. Hamilton W, Watson J, Round A. Rational testing: investigating fatigue in primary care. BMJ 2010;341:502–04.

GUIDE TO ABBREVIATIONS AND ACRONYMS IN THIS UNIT OF *CHECK*

Ach	acetylcholine	MBS	Medicare Benefits Schedule	RDW	red cell distribution width
AChR-Ab	acetylcholine receptor antibody	MCH	mean corpuscular haemoglobin	RNS	repetitive nerve stimulation
ACR	American College of Rheumatology	MCV	mean corpuscular volume	SFEMG	single fibre electromyography
CBT	cognitive behaviour therapy	MuSK-Ab	muscle-specific tyrosine kinase antibodies	SNRI	serotonin and noradrenaline reuptake inhibitor
CFS	chronic fatigue syndrome	NICE	National Institute for Health and Care Excellence	T3	triiodothyronine
CSN	central nervous system	NSAID	non-steroidal anti-inflammatory drug	T4	thyroxine
EPS	electrophysiological studies	PBM	patient blood management	TSH	thyroid stimulating hormone
FBE	full blood evaluation	PBS	Pharmaceutical Benefits Schedule	WPI	widespread pain index
GET	graded exercise therapy				
IVIG	intravenous immunoglobulin				
LFT	liver function test				

CASE 1

TIFFANY IS TIRED EVERY DAY

Tiffany is a university student aged 24 years. She had glandular fever in her first year at university and since then she tires easily. In the last 6 months she has been tired every day. Activities that she once completed easily now leave her feeling exhausted. She often naps in the afternoon but is unable to fall asleep at night. She struggles to complete assignments and has not been able to keep a part-time job. She does not have much social support as her parents have recently separated. She feels lonely and sometimes angry that this is happening to her. She wants to feel better. On examination her temperature is 36.8°C, her colour is normal and her cardiovascular, respiratory and abdominal examination is normal. She has no skin or joint changes. Her weight is stable.

QUESTION 1

What are possible diagnoses?

QUESTION 2

What investigations, if any, would you arrange for Tiffany?

FURTHER INFORMATION

You get the results back from your investigations and they are all normal. You think that Tiffany may have chronic fatigue syndrome (CFS).

QUESTION 3

Why might you think this is CFS?

FURTHER INFORMATION

Tiffany is not happy with the diagnosis of CFS. She feels that there must be something else wrong with her and seems upset as she leaves.

QUESTION 4

What difficulties might be experienced when discussing a diagnosis of CFS with patients?

QUESTION 5

How can you address a patient's concerns about a diagnosis of CFS?

QUESTION 6

What are the current recommended management options for CFS?

CASE 1 ANSWERS

ANSWER 1

Tiffany's main complaint is of fatigue that has worsened over the past 6 months. Conditions that cause fatigue include depression and anxiety, hypothyroidism, diabetes, anaemia, infection, other endocrine disorders such as Addison's disease, inflammatory bowel disease, and liver or renal disease.[1] Substance misuse should also be excluded.

ANSWER 2

The National Institute for Health and Care Excellence (NICE) UK recommends a number of investigations for fatigue (*Table 1*) in cases where chronic fatigue syndrome is suspected. These investigations screen for known organic causes of fatigue and are intended to exclude serious pathology. Clinical judgement will dictate if additional tests are required to exclude other diagnoses.[1]

Table 1. Recommended investigations for fatigue[1]

Investigations
• Urinanalysis (for protein, blood and glucose)
• Full blood count
• Liver function
• Thyroid function (TSH)
• Erythrocyte sedimentation rate
• C-reactive protein
• Random blood glucose
• Serum creatinine
• Screening blood tests for gluten sensitivity
• Serum calcium
• Creatinine kinase
• Serum ferritin levels (for children and young people only)

ANSWER 3

CFS, also referred to as myalgic encephalomyelitis, is a disabling condition.[2] CFS interferes with activities of daily living, causing debilitating fatigue that can be triggered by minimal activity. Patients have other symptoms, such as cognitive impairment, difficulty in sleeping, muscle and joint pains, lymphanopathy, dizziness or nausea, and sore throat.[1,3] CFS is a diagnosis of exclusion but prompt diagnosis can improve outcomes.

NICE guidelines state that a diagnosis of CFS can be made when other possible causes of excessive fatigue have been excluded and symptoms have persisted for more than 4 months in adults or 3 months in children (for children, the diagnosis should be confirmed by a paediatrician).[1] The peak incidence of CFS occurs at the age of 20–40 years and is more common in women.[4] The average duration is 3–9 years.[2] However, some patients may remain unwell for 20–30 years.[5]

The aetiology of CFS is poorly understood and remains controversial.[1] Suggested aetiologies include viral infection, autoimmune, endocrine, genetic and psychiatric causes, including traumatic life experiences.[6–8] The pathophysiology remains unknown.[9]

ANSWER 4

CFS is a diagnosis that can be associated with negative feelings from patients and stigma from the community.[10] As CFS does not have a clear diagnostic marker and has an uncertain aetiology, it can cause difficulty for GPs, patients and the therapeutic relationship. Research has shown that this uncertainty has lead to scepticism about the legitimacy of CFS as a condition, low confidence in healthcare providers to diagnose and manage CFS, and a lack of empathy, disbelief or negative attitudes towards people with CFS.[11]

ANSWER 5

A patient-centred approach can help to explore the feelings of stigmatisation that occur with a CFS diagnosis.[1,6] It may be helpful to explain that although CFS is a diagnosis of exclusion and it is incompletely understood, there is emerging evidence suggesting there may be a triggering event that can cause chronic fatigue in susceptible patients.[12]

It is important to explain the condition and provide education and hope (eg there is considerable research being done on CFS; most people improve over time; there is a better prognosis in younger people). Referrals to specialists or allied health professionals could be considered. Discuss the possibility of setbacks and relapses, and the need for regular review. In Tiffany's case, you could offer to liase with the university if required. In general, discussing return-to-work issues, support groups and encouraging patients to take rest periods could be helpful.

It is important to tell Tiffany that negative test results do not mean 'there is nothing wrong' and you are not negating her symptoms. For more information on patient-centred approaches and care see Resources for doctors.

ANSWER 6

There is no known pharmacological treatment or cure for CFS.[1] Physical and psychological symptoms of CFS, such as nausea or insomnia, should be managed with usual clinical practice. Cognitive behaviour therapy (CBT) and graded exercise therapy (GET) are the current recommend first-line treatments to improve fatigue and quality of life.[1]

CBT has been found to be effective in reducing the symptoms of fatigue. However, additional studies are required, as most studies have been in small groups and evidence for the comparative effectiveness of CBT alone or in combination with other therapies is currently lacking.[13]

Graded exercise programs have been found to improve levels of fatigue but have minimal impact on depression.[14] There is controversy regarding the role of paced exercise, compared with GET or CBT. The PACE study, a randomised controlled trial of 641 patients, found paced exercise had no effect on patient outcomes, compared with CBT or GET, which were both shown to improve outcomes.[15] However, CFS patient groups support the use of paced exercise as there is patient self-reporting of a worsening of symptoms with CBT and GET but not with pacing.[16]

Pacing is often advised along with other self-management strategies,[17] such as goal-setting and self-advocacy training (education and peer mentoring or support groups, encourage optimism and improvement in quality of life 12 months after intervention).[18] Goal setting can be improved by self-reflection using diaries, creative writing, log books or subjective scales.[19] Self advocacy can be improved by encouraging patients to take an active part in designing their own management plan. Self-advocacy programs consist of group or individual programs that support skills to increase self-reliance and reliance on peer networks in solving problems.

A randomised controlled trial of a self-advocacy program showed improvement in self-reported symptom severity and quality-of-life assessments.[20] The program consisted of an initial group where participants set personal goals for wellness and voted on educational topics that would then be used for discussion in illness management groups. This was supported by one-to-one sessions run by peers with CFS in which participants continued to set and attain goals, and also learn and practise strategies for independent living (eg psychological, financial and nutritional skills).

CFS support groups in Australia have information on current self-help courses and resources (see Resources for patients).

When negotiating a treatment plan for patients with CFS, it is important to be aware that there is a high rate of conventional and complementary medicine use by patients, despite limited evidence of their effectiveness.[21] Patients with CFS are more likely to have seen a complementary or alternative healthcare practitioner rather than a psychologist or physiotherapist in a 6-month time frame.[22]

Certain medications and complementary therapies or supplements were highlighted by the NICE 2007 guidelines as not being useful for treatment of CFS. These include monamine oxidase inhibitors, glucocorticoids (such as hydrocortisone), mineralocorticoids (such as fludrocortisone), dexamphetamine, methylphenidate, thyroxine and antiviral agents.[1] There is insufficient evidence to support the use of complementary therapies or supplements such as vitamin B_{12}, vitamin C, co-enzyme Q10, magnesium, multivitamins or minerals in CFS.[1]

In summary, although CBT and GET have been shown to be effective treatments for CFS, further research into management strategies, including therapies favoured by patients with CFS, is warranted.

REFERENCES

1. National Institute for Health and Care Excellence. Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy): diagnosis and management of CFS/ME in adults and children [CG53]. London: NICE, 2007. Available at www.nice.org.uk/NICEMEDIA/LIVE/11824/36193/36193.PDF [Accessed 2 April 2014].
2. Cairns R, Hotopf M. A systematic review describing the prognosis of chronic fatigue syndrome. Occup Med 2005;55:20–31.

3. Fukuda K, Straus SE, Hickie I, et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med 1994;121:953–59.
4. Prins JB, van der Meer JWM, Bleijenberg G. Chronic fatigue syndrome. Lancet 2006;367:346–55.
5. Ax S, Gregg V, Jones D. Chronic fatigue syndrome: illness attributions and perceptions of control. Homeostasis 1998;39:44–51.
6. Arroll M, Arroll B. Chronic fatigue syndrome: a patient-centred approach to management. Aust Fam Physician 2013;42:191–93.
7. Bansal AS, Bradley AS, Bishop KN, Kiani-Alikhan S, Ford B. Chronic fatigue syndrome, the immune system and viral infection. Brain Behav Immun 2012;26:24–31.
8. Hatcher S, House A. Life events, difficulties and dilemmas in the onset of chronic fatigue syndrome: a case-control study. Psychol Med 2013;33:1185–92.
9. Fatigue Expert Group. Conditions commonly associated with fatigue. In: eTG Complete [Internet] Melbourne. Therapeutic Guidelines Ltd, 2014. Available at www.tg.org.au [Accessed 23 April 2014].
10. Dickson A, Knussen C, Flowers P. Stigma and the delegitimation experience: an interpretative phenomenological analysis of people living with chronic fatigue syndrome. Psychol Health 2007;22:851–67.
11. Horton SM, Poland F, Kale S, et al. Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) in adults: a qualitative study of perspectives from professional practice. BMC Fam Pract 2010;11:89. Available at www.ncbi.nlm.nih.gov/pmc/articles/PMC2994803/pdf/1471-2296-11-89.pdf [Accessed 1 April 2014].
12. Van Houdenhove B, Luyten P. Customizing treatment of chronic fatigue syndrome and fibromyalgia: the role of perpetuating factors. Psychosomatics 2008;49:470–77.
13. Price JR, Mitchell E, Tidy E, Hunot V. Cognitive behaviour therapy for chronic fatigue syndrome in adults. Cochrane Database Syst Rev 2008;16:cd001027.
14. Edmonds M, Mcguire H, Price JR. Exercise therapy for chronic fatigue syndrome. Cochrane Database Syst Rev 2004:cd003200.
15. White PD, Goldsmith KA, Johnson AL, et al. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. Lancet 2011;377:823–36.
16. Curruthers B, van de Sande M. International consensus primer for medical practitioners. 2012. Available at sacfs.asn.au/download/me_international_consensus_primer_for_medical_practitioners.pdf [Accessed 11 April 2014].
17. Nijs J, Van Eupen I, Vandecauter J, et al. Can pacing self-management alter physical behavior and symptom severity in chronic fatigue syndrome? A case series. J Rehabil Res Dev 2009;46:985–96.
18. Taylor RR, Thanawala SG, Shirasishi Y, Schoeny ME. Long-term outcomes of an integrative rehabilitation program on quality of life: a follow-up study. J Psychosom Res 2008;61:835–39.
19. South Australian Department of Human Services. Myalgic encephalopathy (ME) and chronic fatigue syndrome (CFS): management guidelines for general practitioners. South Australia: Department of Human Services, Metropolitan Division; 2004. Available at http://sacfs.asn.au/download/guidelines.pdf [Accessed 4th May 2014].
20. Taylor, RR. (2004). Quality of life and symptom severity for individuals with chronic fatigue syndrome: findings from a randomized clinical trial. Am J Occup Ther 2004;58:35–43.
21. Kreijkamp-Kaspers S, Weba Brenu E, Marshall S, Staines D, van Driel M. Treating chronic fatigue syndrome: a study into the scientific evidence for pharmacological treatments. Aust Fam Physician 2011;40:907–12.
22. Sabes-Figuera R, Mccrone P, Hurley M, King M, Donaldson AN, Ridsdale L. The hidden cost of chronic fatigue to patients and their families. BMC Health Serv Res 2012;10:56. Available at www.biomedcentral.com/1472-6963/10/56 [Accessed 1 April 2014].

RESOURCES FOR PATIENTS

- Better Health Channel. Chronic Fatigue Syndrome fact sheet. www.betterhealth.vic.gov.au/bhcv2/bhcarticles.nsf/pages/Chronic_fatigue_syndrome

RESOURCES FOR DOCTORS

- Arroll M, Aroll B. Chronic fatigue syndrome: A patient-centred approach to management. Aust Fam Physician 2013;42:191–93.

CASE 2

AMY HAS TIREDNESS AND PAIN

Amy is 42 years of age. She presents with a 4-year history of worsening lethargy, generalised body aches, poor-quality sleep and difficulty coping to a point where she has stopped working. She feels that her pain has an aching and burning quality associated with mild intermittent paraesthesia. Amy's initial symptoms, which consisted of shoulder and back pain and significant lethargy, commenced after a severe viral illness. Since then, symptoms have slowly worsened and the pain has become more widespread.

Amy has insulin resistance and her BMI is 32 kg/m^2. She was diagnosed with depression after her divorce 5 years ago, and was previously on venlafaxine.

QUESTION 1

What are the possible causes of Amy's symptoms?

QUESTION 2

What further history and examination would you perform for Amy?

FURTHER INFORMATION

Amy does not have a history suggestive of a connective tissue disease; however, she believes that her hands and feet tend to feel swollen. Amy had a sleep study done 2 years ago, which did not show sleep apnoea. She has noticed multiple chemical sensitivities, including perfume, paint and detergents.

Amy is divorced and currently lives with her two children, aged 8 and 12 years. She feels barely able to cope with the housework and walking her children to school. She has significant stress in her life and her ex-husband's new girlfriend does not get along well with Amy's children. Financial stress has been significant since she ceased working as an office administrator 6 months ago. She stopped working as she found it impossible to perform her regular tasks because of her worsening symptoms. She had been jogging regularly but ceased this activity in the last year because of worsening pain and lethargy.

Her current medications include meloxicam 15 mg daily, paracetamol 2 tablets of 665 mg twice daily or as needed, and oxycontin SR 10 mg twice daily.

Amy seems distressed and anxious, but is not depressed. Physical examination is unremarkable and there is no evidence of joint swelling or lymphadenopathy. Her blood pressure is 130/80 mmHg and she has multiple tender points on formal tender-point examination.

QUESTION 3

What investigations would you request?

FURTHER INFORMATION

The results of Amy's blood investigations are:

- full blood evaluation – within normal limits
- renal and liver function – within normal limits
- erythrocyte sedimentation rate – 5 mm/hr [normal 0–25]
- C-reactive protein – 2 mg/L [normal 0–5]
- thyroid function – within normal limits
- creatine kinase – 105 µg/L [normal 0–190]
- vitamin D (25OHD) level – 60 nmol/L [normal 75–250]
- rheumatoid factor <20 kIU/L [normal 0–20]
- antinuclear antibody – negative.

QUESTION 4

What is the diagnosis?

QUESTION 5

What are the pathophysiological mechanisms involved in fibromyalgia?

QUESTION 6

How is fibromyalgia managed? How would you manage Amy?

CASE 2 ANSWERS

ANSWER 1

Fatigue is a common complaint in general practice, experienced by 5–7% of patients.[1] Chronic, widespread musculoskeletal pain is found in up to 10% of the general community[2] and can coexist with fatigue in many chronic illnesses. Conditions to consider that may be possible causes of Amy's symptoms include infections, metabolic and endocrine problems, sleep apnoea, primary insomnia and rheumatological conditions.[3] The non-specific nature of some of Amy's clinical features means that a broad range of problems need to be considered initially. Many of these conditions, such as infection or rheumatological disease, will have more localising features on history and examination. A combination of widespread musculoskeletal pain and fatigue occurring after a significant physical or psychological stressor, however, should raise the possibility of fibromyalgia.

ANSWER 2

On history taking, a full systems review needs to be undertaken. This should include asking questions about gastrointestinal symptoms, urinary symptoms and bleeding history, including menstrual blood loss. Information regarding the quality and length of sleep, recent infections, joint pains or swelling are essential.[1] A full psychosocial history and enquiries regarding mental health problems, including stressful events and mood, need to be included.[1] Information regarding the use of excessive alcohol, smoking history and illicit drug use is important.

Red flags for underlying serious pathology include older age at new symptom onset, weight loss, night pain, focal pain, fevers and sweats, neurological features and history of malignancy.[3]

A cardiovascular, respiratory, abdominal and neurological examination should be performed. A full rheumatological examination looking for features of inflammatory arthritis or connective tissue disease is important. Other bedside tests, including urine analysis and blood pressure measurement, should be checked.[1]

Any widespread musculoskeletal tenderness should be noted if considering a diagnosis of fibromyalgia.

A formal tender-point count using the 18 standardised tender points[4] is not included in the current fibromyalgia diagnostic criteria published by the American College of Rheumatology (ACR) in 2010.[5] Despite this, the finding of widespread musculoskeletal tenderness is informative in reaching a diagnosis of fibromyalgia.

ANSWER 3

Investigations should include blood tests for a full blood evaluation, renal and liver function, erythrocyte sedimentation rate, C-reactive protein, calcium, magnesium and phosphate, thyroid function, creatinine kinase, vitamin D level, rheumatoid factor and antinuclear antibody.[3]

ANSWER 4

The findings are consistent with fibromyalgia. Fibromyalgia does not cause abnormalities that are detectable on standard blood tests; however, it is important to screen for other potential causes of these generalised symptoms. There are no clinical features or pathology results suggestive of an alternative cause for her symptoms at this time. Amy has a low vitamin D level, which should be corrected with oral supplements; however, it is not low enough to be the major cause of her symptoms.

Fibromyalgia is a common condition affecting approximately 2–4% of the population, predominantly women.[6,7] It has characteristic clinical features of widespread musculoskeletal pain and tenderness, fatigue, poor-quality unrefreshing sleep, cognitive disturbances and high levels of distress. It is classified as a central sensitivity syndrome, often associated with similar sensitivity syndromes, including irritable bowel syndrome, temporomandibular joint disorder, recurrent headache and multiple chemical sensitivities.[8]

Fibromyalgia can be diagnosed and managed in the primary care setting, where the general practitioner is uniquely placed to understand the many different factors influencing the patient's wellbeing.

In 2010 the ACR published preliminary diagnostic criteria for fibromyalgia,[5] which were modified in 2011.[9] The criteria are separated into two components: the Widespread Pain Index (WPI), which assesses the extent of pain over the past week, and the symptom severity score, which takes into account fatigue levels, sleep disturbance, cognitive problems and other sensitivity symptoms. These criteria are evaluated by medical practitioners after asking patients to fill in a simple survey. The nature of the assessment helps to conceptualise the symptoms of fibromyalgia on a central sensitisation continuum.[10]

A patient satisfies diagnostic criteria for fibromyalgia if the following three conditions are met:[5]

- WPI ≥7 and symptom severity score ≥5 or WPI = 3–6 and symptom severity score ≥9
- symptoms present at a similar level for at least 3 months
- absence of other disorder(s) that might account for the pain.

ANSWER 5

Fibromyalgia can be thought of as a 'centralised pain state' and is characterised by pain originating or being amplified by changes in the sensory pathways of the central nervous system (CNS).[10] These changes include sensitisation at the dorsal horn level, augmentation and modification of sensory processing in the higher pain centres and altered descending inhibitory pain modulation pathways.[11,12] The results of this abnormal central pain processing includes heightened sensitivity, allodynia (where normally non-painful stimuli result in pain) and other characteristic features such as fatigue, sleep disorder and cognitive disturbances. The development of changes that lead to the clinical syndrome of fibromyalgia seems to occur in genetically predisposed individuals as a maladaptive response to chronic physical or psychological stress.[13]

ANSWER 6

Management of fibromyalgia needs to be multidisciplinary. A management plan needs to include a combination of patient education, an exercise program, pain management psychology and medications.[14,15] The involvement of the patient in their own management is paramount and the success of treatment often hinges on the extent of patient engagement and ownership of their management plan. Regular reviews are an important part of management. Referral to specialists can be made when required.

The general practitioner is the most appropriate and effective person to assess and coordinate ongoing treatment programs for patients with fibromyalgia.

Chronic disease management Medicare Benefits Schedule (MBS) item numbers can be used when planning treatment for patients with fibromyalgia.

The following items could be considered in a management plan.

Patient education

Good patient education is essential in fibromyalgia management.[16,17] Discussion should cover the clinical features and pathophysiology of fibromyalgia and the need for a multidisciplinary treatment approach. It is important to discuss the fact that although fibromyalgia can be disabling, it is not damaging, inflammatory or degenerative in nature, and that with significant patient engagement and compliance, the prognosis is often good.

Exercise

Aerobic exercise has beneficial effects on physical capacity and helps improve symptoms of fibromyalgia. Strength training may also improve some fibromyalgia symptoms.[18] Any exercise program needs to be initiated gently with small amounts of graded, low-impact aerobic activity 3–5 times per week.[14,19] This can be slowly increased over time within tolerance limits. Hydrotherapy, tai chi, qi gong and yoga may be helpful.[14,20]

Psychology

Cognitive behaviour therapy with relaxation or biofeedback results in significant improvements in pain, mood and disability.[21] This will often be an essential enabling step for a patient to engage with a management program. Information about fibromyalgia support groups might be helpful.

Medications

The only medication currently licensed by the Therapeutic Goods Administration (TGA) for use in fibromyalgia is the serotonin and noradrenalin reuptake inhibitor (SNRI) milnacipran, which currently is not available on the Pharmaceutical Benefits Scheme (PBS).

Other medications that have good evidence for benefit in the management of fibromyalgia include amitriptyline and duloxetine, which prevent the reuptake of serotonin and noradrenaline, and improve the function of descending nociceptive inhibitory control pathways in the CNS,[22,23] and the alpha$_2$ delta ligands, gabapentin and pregabalin.[24,25] Non-steroidal anti-inflammatory agents and paracetamol can be modestly helpful in some patients.[26] There

is insufficient evidence that the use of opioids is beneficial in the management of fibromyalgia[27] and reports of reduced effectiveness of opioids in fibromyalgia pain[28] may relate to hyperactivity in the endogenous opioid system in fibromyalgia.[29] There is some evidence that low-dose naltrexone may be helpful in managing fibromyalgia pain.[30]

Management of comorbid conditions

Associated conditions such as depression, anxiety, restless legs and irritable bowel will need to be assessed and managed as appropriate.

Amy needs to be managed using a multimodal approach, including education, psychological support, initiation of an aerobic exercise plan and medication. The aim would be to wean her off opioid analgesia.

REFERENCES

1. Hamilton W, Watson J, Round A. Investigating fatigue in primary care. BMJ. 2010;341:499–504.
2. Gran JT. The epidemiology of chronic generalized musculoskeletal pain. Best practice & research Clinical rheumatology. 2003;17:547–61.
3. Guymer E, Littlejohn G. Fibromyalgia: current diagnosis and management. Expert Rev Clin Immunol 2009;5:181–92.
4. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum 1990;33:160–72.
5. Wolfe F, Clauw DJ, Fitzcharles MA, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res 2010;62:600–10.
6. Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum 1995;38:19–28.
7. Vincent A, Lahr BD, Wolfe F, et al. Prevalence of fibromyalgia: a population-based study in Olmsted County, Minnesota, utilizing the Rochester Epidemiology Project. Arthritis Care Res 2013;65:786–92.
8. Yunus MB. Role of central sensitization in symptoms beyond muscle pain, and the evaluation of a patient with widespread pain. Best Pract Res Clin Rheumatol 2007;21:481–97.
9. Wolfe F, Clauw DJ, Fitzcharles MA, et al. Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia. J Rheumatol 2011;38:1113–22.
10. Clauw DJ. Fibromyalgia: a clinical review. JAMA 2014;311:1547–55.
11. Schmidt-Wilcke T, Clauw DJ. Fibromyalgia: from pathophysiology to therapy. Nature Reviews Rheumatol 2011;7:518–27.
12. Phillips K, Clauw DJ. Central pain mechanisms in chronic pain states – maybe it is all in their head. Best Practice Res Clin Rheumatol 2011;25:141–54.
13. Martinez-Lavin M. Biology and therapy of fibromyalgia. Stress, the stress response system, and fibromyalgia. Arthritis Res Ther 2007;9:216.
14. Fitzcharles MA, Ste-Marie PA, Goldenberg DL, et al. 2012 Canadian Guidelines for the diagnosis and management of fibromyalgia syndrome: Executive summary. Pain Research Manage 2013;18:119–26.
15. Littlejohn GO, Walker J. A realistic approach to managing patients with fibromyalgia. Current Rheumatol Rep 2002;4:286–92.
16. King SJ, Wessel J, Bhambhani Y, Sholter D, Maksymowych W. The effects of exercise and education, individually or combined, in women with fibromyalgia. J Rheumatol 2002;29:2620–27.
17. Rooks DS, Gautam S, Romeling M, et al. Group exercise, education, and combination self-management in women with fibromyalgia: a randomized trial. Arch Int Med 2007;167:2192–200.
18. Busch AJ, Barber KA, Overend TJ, Peloso PM, Schachter CL. Exercise for treating fibromyalgia syndrome. Cochrane Database Syst Rev 2007(4):CD003786. Epub 2007/10/19.
19. Arnold LM, Clauw DJ, Dunegan LJ, Turk DC. A framework for fibromyalgia management for primary care providers. Mayo Clin Proc 2012;87:488–96.
20. Guymer E, Littlejohn G. Fibromylagia. Aust Fam Physician 2013;42:690–94.
21. Glombiewski JA, Sawyer AT, Gutermann J, Koenig K, Rief W, Hofmann SG. Psychological treatments for fibromyalgia: a meta-analysis. Pain 2010;151:280–95.
22. Hauser W, Petzke F, Uceyler N, Sommer C. Comparative efficacy and acceptability of amitriptyline, duloxetine and milnacipran in fibromyalgia syndrome: a systematic review with meta-analysis. Rheumatology (Oxford). 2011;50:532–43.
23. Hauser W, Bernardy K, Uceyler N, Sommer C. Treatment of fibromyalgia syndrome with antidepressants: a meta-analysis. JAMA 2009;301:198–209.
24. Arnold LM, Goldenberg DL, Stanford SB, et al. Gabapentin in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled, multicenter trial. Arthritis Rheum 2007;56:1336–44.
25. Crofford LJ, Rowbotham MC, Mease PJ, et al. Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial. Arthritis Rheumatism 2005;52:1264–73.
26. Clauw DJ. Pain management: Fibromyalgia drugs are 'as good as it gets' in chronic pain. Nature Rev Rheumatol 2010;6:439–40.
27. Ngian GS, Guymer EK, Littlejohn GO. The use of opioids in fibromyalgia. Int J Rheum Dis 2011;14:6–11.
28. Brummett CM, Janda AM, Schueller CM, et al. Survey criteria for fibromyalgia independently predict increased postoperative opioid consumption after lower-extremity joint arthroplasty: a prospective, observational cohort study. Anesthesiology 2013;119:1434–43.
29. Harris RE, Clauw DJ, Scott DJ, McLean SA, Gracely RH, Zubieta JK. Decreased central mu-opioid receptor availability in fibromyalgia. J Neuroscience 2007;27:10000–06.
30. Younger J, Noor N, McCue R, Mackey S. Low-dose naltrexone for the treatment of fibromyalgia: findings of a small, randomized, double-blind, placebo-controlled, counterbalanced, crossover trial assessing daily pain levels. Arthritis Rheum 2013;65:529–38.

CASE 3

JANET HAS SEVERE FATIGUE

Janet is an accountant aged 43 years. She has a history of coeliac disease (quiescent on the most recent endoscopy) and depression, for which she remains on a low dose of a selective serotonin reuptake inhibitor and is well managed. Her other medications are calcium and vitamin D for previously diagnosed malabsorption and a family history of osteoporosis.

Over the past 6 months, Janet has experienced severe fatigue. She feels this is negatively affecting her ability to monitor complex financial transactions at work and keep up with her teenage children. Specific questioning reveals additional symptoms, including weight gain of 6 kg, constipation and heavier periods than usual. Her work and home life are often hectic but Janet cannot identify any new psychosocial stressors that could be affecting her life. She hopes to find a cause for her fatigue so that she can 'get on with life'.

QUESTION 1

What is the most likely cause of her fatigue? What differential diagnoses need to be excluded?

QUESTION 2

What investigations should be performed?

QUESTION 3

If all the investigations are normal, what else needs to be considered?

FURTHER INFORMATION

Janet's serum thyroid stimulating hormone (TSH) is markedly elevated at 58 mU/L (reference range 0.4–4.5 mU/L). Mild anaemia (haemoglobin 115 g/dL), mild hyponatraemia (132 mmol/L) and a slightly increased serum creatinine (81 µg/L, compared with 63 µg/L when checked 2 years earlier) are also present. The results of other investigations are within normal limits.

QUESTION 4

Are any other investigations required?

QUESTION 5

What treatment should be commenced? What is the therapeutic target?

QUESTION 6

Are there any circumstances where approach or goals of hypothyroidism treatment need to be altered?

FURTHER INFORMATION

After 3 months, and despite full-dose levothyroxine therapy (including a small dose increase), Janet remains tired. Her periods are less heavy and she has lost 3 kg of excess weight. Her serum TSH has improved but continues to be elevated at 21 mU/L, indicating continued hypothyroidism. Other laboratory abnormalities have returned to baseline.

QUESTION 7

Why isn't the treatment working?

QUESTION 8

What future surveillance, if any, should be performed?

QUESTION 9

Is there any role for T3 in hypothyroidism treatment?

QUESTION 10

When should a specialist endocrinologist or physician's opinion be sought for hypothyroidism?

CASE 3 ANSWERS

ANSWER 1

The combination of fatigue, impaired cognition, weight gain, constipation and menorrhagia suggest hypothyroidism as a likely cause of Janet's fatigue.[1] This is particularly so given her pre-existing autoimmune condition (coeliac disease).[1] Other clinical features of hypothyroidism are outlined in *Table 1*. Recurrent depression is a possible cause of her fatigue but is unlikely because of the absence of specific depressive symptoms. Severe anaemia, which could be a result of iron deficiency from menorrhagia or pernicious anaemia as a second autoimmune condition, is an important differential diagnosis.[1]

A flare-up of coeliac disease is unlikely if Janet is adhering to a gluten-free diet. Symptomatic diabetes mellitus would be expected to be associated with weight loss. Addison's disease (primary adrenal failure) is associated with weight loss and increased skin pigmentation. Heart, liver and renal failure, or nephrotic syndrome could present with weight gain, although pitting oedema and other likely pointers would be expected on history or examination. While Janet is menstruating regularly, pregnancy is easy to exclude and must not be missed. Obstructive sleep apnoea can be screened for on history. Chronic fatigue syndrome is a diagnosis of exclusion.[2]

Table 1: Possible signs and symptoms of hypothyroidism

System	Symptoms	Signs
General	Tiredness Cold intolerance Weight gain Hoarse voice	Mild hypothermia Thyroid findings (goitre or atrophic thyroid with Hashimoto thyroiditis, surgical scar)
Dermatological	Dry skin Alopecia	Dry, coarse skin, occasionally yellow-tinged Cool extremities Myxoedema (puffy face, hands and feet) Alopecia Brittle nails
Neurological	Poor concentration Poor memory Depression Paraesthesia Impaired hearing	Delayed deep tendon reflex relaxation Carpal tunnel syndrome Slow dysarthric speech
Musculoskeletal	Weakness Myalgias Arthralgias	
Cardiorespiratory	Dyspnoea	Bradycardia Diastolic hypertension Pericardial effusion Pleural effusion
Gastrointestinal	Constipation Poor appetite	
Reproductive	Menorrhagia Infertility	

ANSWER 2

Serum TSH is the screening test for primary hypothyroidism.[1] It is the only test for thyroid disease funded by the Medicare Benefits Schedule (MBS) when there is no previous history of thyroid problems.[3]

Additional investigations may be required to exclude differential diagnoses. For example, a full blood evaluation (FBE) will assess for anaemia. Electrolytes and liver function tests will detect increased creatinine resulting from chronic kidney disease, hypoalbuminaemia from chronic disease, liver disease, nephrotic syndrome, hyperglycaemia and hypercalcaemia. Hyponatraemia can be caused by hypothyroidism. Alternatively, hyponatraemia and hyperkalaemia can be associated with Addison's disease, which is rare but important not to miss because treatment of hypothyroidism in the presence of untreated adrenal insufficiency can lead to adrenal crisis.[1] Point-of-care or formal beta-human chorionic gonadotropin will rule out pregnancy.

ANSWER 3

A normal serum TSH finding rules out primary hypothyroidism,[4] which accounts for most cases of hypothyroidism (*Table 2*). However, if the pre-test probability for hypothyroidism is very high, central hypothyroidism (secondary to pituitary or hypothalamic disease) should be considered. In this case, serum free thyroid hormone (free triiodothyronine [T3] and free thyroxine [T4]) levels will be low while serum TSH may be low, normal or minimally above the reference range.[1,4]

Supplementary history and physical examination (if not previously performed) should include alcohol and drug intake (including over-the-counter and alternative therapies), sleep history and assessment for any potential rheumatological (synovitis, rashes) or neurological conditions, including signs of a pituitary tumour and abnormal tendon reflexes. The neck and thyroid should be examined and blood pressure and weight measured.

Screening for other organic disease that could be considered includes C-reactive protein and erythrocyte sedimentation rate.

Table 2: Causes of hypothyroidism

Classification	Cause
Primary	Hashimoto thyroiditis Post-ablative treatment (either radio-iodine or thyroidectomy) Drugs (carbimazole, propylthiouracil, lithium, interferon, amiodarone, rifampicin, tyrosine kinase inhibitors) Subacute thyroiditis (transient) Iodine deficiency (rare in Australia) Excessive iodine intake (kelp, radiocontrast dyes) Neonatal/congenital (TSH receptor blocking antibodies from mother, inborn errors of thyroid hormone synthesis)
Secondary/tertiary	Hypopituitarism Hypothalamic dysfunction
Other	Peripheral resistance to thyroid hormones

ANSWER 4

Other investigations are probably not required in Janet's case. Free T3 and free T4 levels could be assessed but, given Janet's symptoms and markedly elevated TSH, these are likely to be below the reference range and will not change management. The presence of thyroid autoantibody (anti-thyroid peroxidase) levels will confirm the autoimmune nature of thyroid damage (ie Hashimoto thyroiditis). The likelihood of finding elevated levels of autoantibodies is almost certain as Hashimoto thyroiditis is the main cause of spontaneous hypothyroidism in Australia,[5] Janet's hypothyroidism is severe and she already has an autoimmune disorder. Ultrasonography is not indicated unless there are palpable thyroid nodules or cervical lymphadenopathy.[6] There is no role for nuclear thyroid scanning (uptake of pertechtnate will be high) or serum thyroglobulin in this case. Although hypothyroidism causes hypercholesterolaemia,[7] measurement of fasting lipids would only change management if the hypothyroidism were so mild or subclinical that the indication for treatment of hypothyroidism was uncertain. If the clinical and biochemical hypothyroidism had not been so severe (eg a moderately high TSH level identified on screening), a strategy of retesting the serum TSH 2–8 weeks later would be reasonable to ensure the TSH is persistently elevated. Such an approach in Janet's case would simply prolong the hypothyroidism.

The mild anaemia, hyponatraemia and increase in creatinine could be explained by the hypothyroidism. As the abnormalities are mild, further laboratory testing at this stage is not necessary; however, they warrant consideration and follow-up assessment. The anaemia warrants immediate further testing if the mean cell volume is either low (iron deficiency) or high (B_{12} deficiency). Selective serotonin reuptake inhibitors can also induce hyponatraemia[8] but there is no need to cease this medication because the hyponatraemia is mild and likely to be reversed with treatment of hypothyroidism. Supplementary history and physical examination should screen for systemic rheumatological conditions such as systemic lupus erythematosis.[1] A urine dipstick is useful to rule out significant proteinuria or haematuria, which would be present in a coexisting glomerulonephritis. In the absence of the above problems, repeat testing should be performed after commencement of levothyroxine to ensure that the haemoglobin, sodium and creatinine levels have returned to normal with therapy.

ANSWER 5

Levothyroxine should be commenced to relieve symptoms and restore and maintain a euthyroid state.[9] Standard initial replacement doses equate to 1.6 µg/kg of body weight per day, rounded to the nearest 25 µg (ie 100 µg per day for a 60 kg person).[10] For most people being treated for hypothyroidism, the usual dose of thyroxine will be up to 200 µg once daily.[10,11] Full treatment dose could be commenced for Janet and treatment will be life-long.[9,11,13]

Levothyroxine should be taken on an empty stomach,[10,11] preferably 1 hour before breakfast.[12] If this is not possible, 3–4 hours after food is reasonable. The levothyroxine should be stored in the refrigerator, except for in-use blister strips, which may be stored unrefrigerated (<25ºC) and protected from light for up to 2 weeks (or in hot climates, stored in the refrigerator).[11] Two brands of levothyroxine, made by the same manufacturer, are available in Australia and are identical.[14]

Thyroid function tests can be repeated 6–8 weeks after commencing treatment,[10] unless symptoms of over-replacement/hyperthyroidism occur in the meantime. Target levels of serum TSH are not clearly defined but most endocrinologists aim for levels of 1.0–1.9 mU/L (or less commonly <3 mU/L).[15] *Therapeutic Guidelines–Endocrinology* recommend TSH levels of 0.5–2 mU/L, a range that approximates TSH concentration in the general population.[11]

If fine titration of dosing is required or, for convenience of not having too many tablets of different strengths, doses can be alternated or given on defined days (ie 150 µg per day is equivalent to 100 µg on 4 days plus 200 µg on 3 days, or 200 µg on 5 days plus two drug-free days). This flexibility of dosing is possible because of the very long half-life of levothyroxine. In cases of extreme non-adherence, another approach is once weekly dosing (under pharmacist supervision if required).[16]

ANSWER 6

Management of hypothyroidism and treatment goals need to be modified for patients with cardiovascular disease or those aged >60 years. These patients should be commenced on lower than full maintenance doses because of the risk of exacerbating heart disease on levothyroxine commencement.[10] A starting dose of 50 µg per day would be reasonable in most cases. If there is any concern about severe exacerbation of cardiovascular disease, or in the extreme elderly, even lower doses (eg 25 µg per day) could be commenced.[17] Commencement of lower doses is not required following thyroidectomy in euthyroid patients; near or full-dose replacement should be commenced for these patients. Treatment goals are often relaxed with advancing age as the normal TSH range also increases.[15]

For women with pre-existing hypothyroidism, the dose of levothyroxine should be increased by 30–50% on confirmation of pregnancy, because of increased thyroid hormone requirements.[18] The target TSH range is 0.1–2.5 mU/L in the first trimester and 0.1–3.0 mU/L in later pregnancy.[19] It is important to monitor TSH levels regularly during pregnancy, particularly in the first trimester. There is some evidence for treating patients with euthyroid Hashimoto thyroiditis (ie those with thyroid autoantibodies) with low-dose thyroxine (eg 50 µg per day) throughout pregnancy, especially if there is a history of miscarriage. [20]

Serum TSH should not be used to monitor therapy in patients with secondary hypothyroidism due to pituitary or hypothalamic disorders.[1] Serum free T4 should be titrated to a mid–high normal reference range.[21] As with primary adrenal insufficiency, it is important to rule out secondary adrenal deficiency prior to commencement of levothyroxine treatment.

In subclinical hypothyroidism (ie mildly elevated TSH, which is often asymptomatic, with a normal T4) the approach to treatment is controversial.[9] Treatment in more severe disease (ie serum TSH

>10 mU/L) is usually recommended.[9,22] Treatment at lower TSH levels may be justified if progressive deterioration is occurring in the presence of thyroid autoantibodies or as a trial where hypothyroid symptoms may be present.[22] In such cases, lower doses of levothyroxine (eg 25–75 µg daily) than those used for overt hypothyroidism, can be given.[1]

Patients with high-risk, differentiated thyroid cancer (high-risk papillary and follicular cancer) may be treated with higher doses levothyroxine to decrease serum TSH levels to <0.1 mU/L, because of improved survival with this approach.[23]

ANSWER 7

The five most common reasons for treatment failure are:[11]

- inadequate prescribed dose of levothyroxine
- incomplete adherence to medication
- incorrect administration or storage of levothyroxine
- interfering medications
- impaired absorption of levothyroxine.

In Janet's case, interfering medications, in particular, concomitant calcium supplementation, is the prime candidate.[11] If required, the calcium should be spaced as far as possible from levothyroxine. Other medications that can interfere with levothyroxine pharmacokinetics are listed in *Table 3*. Uncontrolled coeliac disease could cause impaired absorption of levothyroxine;[11] this is unlikely given that Janet's coeliac disease has been well controlled but could be assessed clinically and by checking for coeliac antibodies.

If there is continued difficulty in normalising the serum TSH concentration, obtaining Janet's serum free T4 (and free T3) level may be helpful. A high serum TSH but high normal or frankly high serum free T4 is most probably due to non-adherence with administration shortly before the blood test. Rare, organic causes for the inability to normalise serum TSH concentration include interfering (ie heterophile) antibodies and coxisting pituitary tumours secreting TSH.

Table 3: Drugs interfering with levothyroxine pharmacokinetics

Lower absorption	Increased thyroxine requirements
Calcium supplements	Phenytoin
Iron supplements	Phenobarbital
Cholestyramine	Carbamazepine
Aluminium hydroxide	Rifampin
Expresso coffee	Tyrosine kinase inhibitors

ANSWER 8

Once rendered biochemically euthyroid on levothyroxine, the next serum TSH level could be performed after 6 months, provided Janet is asymptomatic. Thereafter, thyroid review and testing could be 12-monthly.[11] Repeat testing for anti-thyroid peroxidase antibodies, if tested initially, are not required. Thyroid imaging is not recommended unless thyroid nodules or lymphadenopathy are detected clinically.[6]

ANSWER 9

Currently, there is no role for T3 in the management of hypothyroidism. Most circulating T3 is formed from deiodination of circulating T4[24] and since the 1970s synthetic levothyroxine has been the treatment of choice for thyroid hormone replacement. While it is true that a subset of patients on appropriate levothyroxine therapy remain symptomatic, the difficulty is that hypothyroid symptoms are often non-specific and are very common in the wider euthyroid population.[25] A 1999 study assessing 33 patients claimed improved mood and neuropsychological function after short-term combination T3/T4 treatment;[23] these results have not been replicated. Further research into potential combination therapies, and whether identifiable patient subgroups might benefit, are ongoing. Oral T3 is not available on the Pharmaceutical Benefits Scheme (PBS) for the treatment of hypothyroidism. Desiccated thyroid hormone products are not registered with the Therapeutic Goods Administration (TGA).

ANSWER 10

GPs can manage most cases of hypothyroidism. The American Thyroid Association and American Association of Clinical Endocrinologists recommend the following groups of patients with hypothyroidism be managed in consultation with an endocrinologist or specialist physician:[1]

- children and infants
- patients in whom it is difficult to render and maintain a euthyroid state
- pregnant women
- women planning conception
- patients with cardiac disease
- patients with a goiter, nodule or other structural changes in the thyroid gland
- patients with other endocrine disease such as adrenal and pituitary disorders
- patients with an unusual constellation of thyroid function test results
- patients with unusual causes of hypothyroidism.

REFERENCES

1. Garber JR, Cobin RH, Gharib H, et al. Clinical practice guidelines for hypothyroidism in adults. Thyroid 2012;22:1200–35.
2. National Institute for Health and Care Excellence. Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy): diagnosis and management of CFS/ME in adults and children. London: NICE, 2007.
3. Thyroid WA Support Group. Thyroid function tests. Available at http://thyroidwa.com/the-thyroid/tests-and-diagnoses/thyroid-function-test.html [Accessed 5 May 2014].
4. Mortimer RH. Abnormal laboratory results: thyoid function tests. Aust Presc 2001;34:12–15.
5. Topliss DJ, Eastwell CJ. Diagnosis and management of hyperthyroidism and hypothyroidism. MJA 2004;180:186–93.
6. So M, MacIsaac R, Grossman M. Hypothyroidism: investigation and management. Aust Fam Physician 2012;41:556–62.

7. Duntas LH, Brenta G. The effect of thyroid disorders on lipid levels and metabolism. Med Clin N Am 96 2012;96:269–81.
8. Fourlanos S, Greenberg P. Managing drug-induced hyponatraemia. Aust Prescr 2003;26:114–17.
9. Rossi S, editor. Hypothyroidism. In: Australian Medicines Handbook. Adelaide: Australian Medicines Handbook Pty Ltd, 2014.
10. Rossi S, editor. Thyroxine. In: Australian Medicines Handbook. Adelaide: Australian Medicines Handbook Pty Ltd, 2014.
11. Endocrinology Expert Group. Treating hypothyroidism In: eTG Complete [Internet] Melbourne: Therapeutic Guidelines Ltd, 2014. Available at www.tg.org.au [Accessed 2 April 2014].
12. Bach-Huynh TG, Nayak B, Loh J, et al. Timing of levothyroxine administration affects serum thyrotropin concentration. J Clin Endocrin Metab 2009;94:3905–12.
13. Thyroid Disease Manager. Managing primary hypothyroidism. Available at www.thyroidmanager.org/algorithm/managing-primary-hypothyroidism/ [Accessed 5 May 2014].
14. Davoren P. Modern management of thyroid replacement therapy. Aust Prescr 2008;31:159–61.
15. Burch HB, Burman KD, Cooper DS, et al. A 2013 Survey of clinical practice patterns in the management of primary hypothyroidism. J Clin Endocrin Metab 2014:jc20141046.
16. Grebe SK, Cooke RR, Ford HC, et al. Treatment of hypothyroidism with once weekly thyroxine. J Clin Endcorin Metab 1997;82:870–75.
17. Biondi B, Wartofsky L. Treatment with thyroid hormone. Endocr Rev 2014:er20131083.
18. Alexander EK, Marqusee E, Lawrence J, et al. Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. N Eng J Med 2004;351:241–49.
19. Stagnaro-Green A, Abalovich M, Alexander E, et al. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid 2011;21:1081–25.
20. Negro R, Formoso G, Mangieri T, et al. Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications. J Clin Endocr Metab 2006;91:2587–91.
21. Roberts CGP, Ladenson PW. Hypothyroidism. Lancet 2004;363:793–803
22. Cooper DS, Biondi B. Subclinical thyroid disease. Lancet 2012;379:1142–54.
23. McLeod DS, Sawka AM, Cooper DS. Controversies in primary treatment of low-risk papillary thyroid cancer. Lancet 2013;381:1046–57.
24. Braverman LE, Ingbar SH, Sterling K. Conversion of thyroxine (T4) to triiodothyronine (T3) in athyreotic human subjects. J Clin Invest 1970;49:855–64.
25. Canaris GJ, Manowitz NR, Mayor G, et al. The Colorado thyroid disease prevalence study. Arch Int Med 2000;160:526–34.

RESOURCES FOR PATIENTS

- The American Thyroid Association has a large number of patient resources on thyroid disease. www.thyroid.org
- The Hormone Health Network is affiliated with the US Endocrine Society and has a comprehensive range of patient resources on many endocrine disorders. www.hormone.org

RESOURCES FOR DOCTORS

- Thyroid Disease Manager is a free, online, regularly updated textbook with comprehensive coverage of thyroid disease. www.thyroidmanager.org. It is part of a wider endocrinology project called Endotext: www.endotext.org.
- The American Thyroid Association freely provides their treatment guidelines for a range of thyroid disorders, in addition to other thyroid-related resources. www.thyroid.org
- Therapeutic Guidelines remains an excellent Australian medical resource, including the sections on thyroid disease. A subscription is required. www.tg.org.au
- In 2011 the Endocrine Society of Australia produced a position statement on desiccated thyroid or thyroid extract. www.endocrinesociety.org.au

CASE 4

JOHN IS BREATHLESS ON MILD EXERTION

John is an executive aged 58 years. He presents reporting gradual onset of fatigue over the past couple of months. More recently, he has been breathless on mild exertion. He has been well in the past, apart from some sporting injuries and ongoing musculoskeletal pain for which he takes daily non-steroidal anti-inflammatory drugs (NSAIDs). Systematic enquiry elicits no other symptoms. In particular, there has been no change in his bowel habits or the colour of his motions. He follows a vegetarian diet. Physical examination demonstrates conjunctival pallor but no other abnormality.

QUESTION 1

What tests are appropriate at this point?

FURTHER INFORMATION

A full blood evaluation (FBE) shows the following results:

- haemoglobin – 78 g/L (normal 135–175)
- mean corpuscular volume (MCV) – 70 fL (normal 80–100)
- mean corpuscular haemoglobin (MCH) – 16.8 pg (normal 27–33)
- blood film comment: hypochromic
- red cell distribution width (RDW) – 18% (normal 12–15)
- white cell count and platelet count – normal.

QUESTION 2

What type of anaemia is this likely to be and what further blood tests are indicated?

FURTHER INFORMATION

Iron studies are requested and show the following results:

- serum ferritin – 9 µg/L (normal 30–300 µg/L)
- serum iron – 4 µmol/L (normal 5–30 µmol/L)
- total iron-binding capacity – 90 µmol/L (normal 46–70 nmol/L)
- transferrin saturation – 5% (normal 10–40%).

QUESTION 3

What do these results indicate?

FURTHER INFORMATION

John has not eaten meat for 20 years.

QUESTION 4

Is it reasonable to accept that the iron deficiency is a result of a long-term vegetarian diet? What further investigations, if any, should be undertaken at this point?

QUESTION 5

Could John's daily use of NSAIDs have a bearing on this presentation?

QUESTION 6

What conditions can be associated with malabsorption resulting in this type of anaemia?

FURTHER INFORMATION

Colonoscopy reveals a carcinoma at the caecal pole and biopsies confirm adenocarcinoma. John is referred to a surgeon for right hemicolectomy. Surgery is scheduled in 2 weeks. He is still very fatigued.

QUESTION 7

What is the best way of dealing with John's anaemia, to improve his fitness for surgery and quality of life?

CASE 4 ANSWERS

ANSWER 1

John's fatigue and conjunctival pallor suggest anaemia so a FBE is an appropriate first-line test.[1] His vegetarian diet places him at risk of iron deficiency anaemia, so iron studies are warranted regardless of the FBE results, as iron deficiency without anaemia can cause fatigue and decreased physical performance.

ANSWER 2

This is a hypochromic microcytic anaemia. Although this type of blood film can be associated with the anaemia of chronic disease/inflammation, or thalassaemia[2] and sideroblastic anaemia,[3] the most likely cause of this blood picture is iron deficiency. It is appropriate to order iron studies as the next line of investigation.

ANSWER 3

These results confirm that the anaemia is indeed due to iron deficiency. In particular, the low serum ferritin is indicative of low iron stores.[1] No other condition leads to reduced ferritin levels.[1]

Serum iron is not a reliable indicator of iron deficiency.[4] Total iron binding capacity is elevated in iron deficiency and iron saturation is decreased. The amount of stainable iron in the bone marrow is decreased, but a bone marrow biopsy is rarely needed to make the diagnosis. Occasionally, ferritin levels can be falsely elevated as it is an acute-phase reactant in inflammation, chronic liver disease and malignancy.[4] Markers such as C-reactive protein may help identify coexisting inflammation.[5]

ANSWER 4

More than 10% of the world population is iron deficient.[5] Causes include poor intake of dietary iron, heavy menstrual loss, loss associated with childbirth and breastfeeding, and chronic parasitic infection.[1] Vegetarians are more likely to be iron deficient than people who eat meat.[1] However, in Australia, an otherwise healthy vegetarian man should be investigated to exclude gastrointestinal pathology causing iron deficiency and this should take the form of endoscopy and colonoscopy.[5] Poor oral intake is not an adequate explanation.[1] Faecal occult blood testing is a screening test that is appropriate only for asymptomatic people and not in the presence of gastrointestinal symptoms, rectal bleeding or iron deficiency anaemia, as further investigation will be required, even if the faecal occult blood test is negative.[6]

If endoscopy and colonoscopy do not provide a diagnosis, John should have a small bowel capsule study to exclude small bowel pathology,[5] including benign and malignant small bowel tumours, angiodysplasia, Crohn's disease and, on occasion, small bowel strictures related to NSAID use. A small bowel capsule study is appropriate only in a patient who has already had the more common causes of blood loss ruled out by an endoscopy and colonoscopy.

A Medicare rebate for the capsule study is not available unless endoscopy and colonoscopy have been performed. There was a time constraint attached but this has been removed.

It should be remembered that regular blood donation can, over years, lead to iron deficiency; however, assessment for other causes is still required.[7]

ANSWER 5

John reports daily use of NSAIDs, which can be associated with gastric ulceration, erosions and chronic gastric blood loss.[1] It can also cause small bowel ulceration and strictures, which may not cause any pain but can present as anaemia from chronic blood loss. Therefore, chronic use of NSAIDs is a possible reason for the anaemia[1] but further investigation is required.

ANSWER 6

Malabsorption is a cause of iron deficiency but it can occur in coeliac disease[1] and in achlorhydria.[1]

Coeliac disease affects about 1% of the Australian population.[8] Iron is absorbed in the upper small intestine and is best absorbed in an acidic environment.[1] Coeliac disease affects the proximal small intestine, so iron deficiency is a common presentation with or without gastrointestinal symptoms. Therefore, it is appropriate to perform coeliac serology or, alternatively, a small intestine biopsy at the time of endoscopy, when investigating iron deficiency.[7] About one-third of the Australian population has at least one coeliac gene so a positive gene test is not helpful in making a diagnosis. However, a negative gene test can be helpful in the setting of an equivocal small intestine biopsy, ruling out coeliac disease.

Achlorhydria occurs in atrophic gastritis,[1] which is associated with pernicious anaemia, and can also occur with *Helicobacter pylori* gastritis. Achlorhydia has also been described as arising from long-term use of proton-pump inhibitors.[9]

Some people who have had bariatric surgery may fail to absorb iron.

It is important to note that a significant percentage of people who have an abnormality on gastroscopy, when investigated for iron deficiency, have colonic pathology, including cancer.[1] Therefore it is not appropriate to limit investigation to the upper gastrointestinal tract.[7]

Malignancy at any site in the gastrointestinal tract, reflux oesophagitis, oesophageal varices and angiodysplasia can lead to iron deficiency through chronic blood loss.[1] Benign gastric and duodenal ulcers bleed acutely, resulting in anaemia but not iron deficiency. An old axiom states that 'ulcers gush, cancers ooze' and it is the slow ooze that results in iron deficiency anaemia. Iron deficiency is common in inflammatory bowel disease,[1] but it would be unusual, although not impossible, for there to be no gastrointestinal symptoms.

Premenopausal women may have iron deficiency anaemia as a result of gynaecological blood loss and increased requirements associated with pregnancy, particularly coupled with poor oral iron intake.[1] Gastrointestinal investigations may not be appropriate in all cases, but coeliac disease should be excluded and endoscopy and colonoscopy considered if there is clinical doubt, gastrointestinal symptoms or failure to respond to an appropriate period of oral iron supplementation. Current British guidelines recommend oesophageal gastroduodenoscopy for premenopausal women with iron deficiency anaemia and upper gastrointestinal symptoms, to check for possible upper gastrointestinal cancer.[7]

ANSWER 7

Investigation and management of iron deficiency are parallel strands of care. Iron therapy should be initiated while assessment of the cause is being undertaken.

For most patients the best first-line option for the treatment of iron deficiency is oral iron supplementation. Blood transfusion is not usually appropriate unless an immediate increase in oxygen delivery is required, such as when the patient is experiencing end organ compromise (eg angina or cardiac failure) or iron deficiency anaemia is complicated by serious, acute ongoing bleeding.[9] In Australia, oral iron preparations take the form of ferrous salts (sulphate, gluconate and fumarate) and include tablets and liquid preparations. The usual recommended dose of oral iron for the treatment of iron deficiency anaemia in adults is 100–200 mg of elemental iron daily in 2–3 divided doses.[5] When given at equivalent elemental iron doses, different oral iron salts have similar efficacy and tolerability.[5] Less potent oral therapy may not cause side effects but may not correct the iron deficiency. Iron in multivitamins is insufficient. John should be warned that bowel motions will become black and that oral iron can cause side effects, particularly constipation, diarrhoea and nausea.[10] Haemoglobin levels usually rise by 1–2 g/L daily or 20 g/L over 3–4 weeks.[10]

Taking iron supplements on an empty stomach, although generally advised, is associated with an increased rate of gastrointestinal side effects.[11] Compliance may be improved by suggesting the patient take the supplement with food.[11] Coffee,[11] tea,[11]calcium supplements,[11] antacids and some medications, for example quinolones (eg ciprofloxacin),[4] can impair iron absorption.

For patients with John's degree of iron deficiency, it is necessary to emphasise that they may require daily therapy for 3–6 months after haemoglobin levels have returned to normal to replenish stores.[4,8] For John, this is complicated by his impending surgery, which will be associated with further iron loss, and an infusion of iron may be more appropriate. The new National Patient Blood Management (PBM) Guidelines[12] support the use of intravenous iron when there is a short time before non-deferrable surgery to minimse the risk of red cell transfusion, which is associated with an increased risk of morbidity, mortality and length of stay. The important role of the GP in PBM has recently been highlighted. Many hospitals are now implementing programs to improve management of pre-operative anaemia, including timely access to intravenous iron when needed. An iron infusion is also useful if oral iron causes unacceptable side effects, if compliance is poor, if there is malabsorption with ongoing iron losses exceeding absorptive capacity, and where there is a clinical need for rapid iron supply to help prevent transfusion/decompensation.[10,11]

Intramuscular injections of iron are not adequately absorbed, stain the skin with a greyish discolouration and occasionally cause palpable masses. There is also a possible association with sarcoma. Its use, therefore, is discouraged unless other approaches cannot be practically delivered (eg when parenteral iron is indicated in remote settings).

Iron dextran is associated with a significant risk of anaphylaxis (approximately 0.61%) and is no longer used.

Two parenteral forms of iron are available in Australia on authority script: iron polymaltose and iron sucrose. The latter has PBS approval only for patients with chronic kidney disease on erythropoietin who have had a systemic reaction to polymaltose. The rate of anaphylaxis associated with these preparations is low (<0.1%); however, about one-quarter of patients report influenza-like symptoms for about 2 days after the infusion. Ferric carboxymaltose is an alternative parenteral preparation and can be given more quickly but it is not on the Pharmaceutical Benefits Schedule (PBS) in Australia.[13] Some hospital drug committees have approved the use of ferric carboxymaltose (eg for day patients) as it allows a large dose of iron to be given over 15 minutes.

Lastly, a discussion about diet and non-haem sources of iron would be useful in John's case.

REFERENCES

1. Gastroenterological Society of Australia. Management of iron deficiency. In: Iron Deficiency, 2nd edn. Melbourne: Digestive Health Foundation, 2011. Available at www.gesa.org.au [Accessed 7 April 2014].
2. Urrechaga E, Borque L, Escanero JF. The role of automated measurement of RBC subpopulations in differential diagnosis of microcytic anemia and beta-thalassemia screening. Am J Clin Pathol 2011;135:374–79. Available at http://ajcp.ascpjournals.org/content/135/3/374.full.pdf [Accessed 7 May 2014].
3. Cullis JO. Diagnosis and management of anaemia of chronic disease: current status. Br J Haematol 2011;154:289–300. Available at http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2011.08741.x/pdf [Accessed 7 May 2014].
4. Gastrointestinal Expert Group. Iron deficiency In: eTG Complete [internet] Melbourne: Therapeutic Guidelines, 2014. Available at www.tg.org.au [Accessed 26 March 2014].
5. Pasricha SR, Flecknoe-Brown SC, Allen KJ, et al. Diagnosis and management of iron deficiency anaemia: a clinical update. Med J Aust 2010;193:525–32.
6. Friedman A, Chan A, Chin LC, et al. Use and abuse of faecal occult blood tests in an acute hospital inpatient setting. Intern Med J 2010;40:107–11.
7. Goddard AF, James MW, McIntyre AS, Scott BB. Guidelines for the management of iron deficiency anaemia. Gut 2011;60:1309–16. Available at www.bsg.org.uk/images/stories/docs/clinical/guidelines/sbn/bsg_ida_2011.pdf [Accessed 23 April 2014].
8. Anderson RP. Coeliac disease is on the rise. Med J Aust 2011;194:278–79.
9. Kohli DR, editor. Achloryhdia treatment and management. Medscape: Drugs Dis Proc 2013. Available at http://emedicine.medscape.com/article/170066-overview [Accessed 23 April 2014].
10. Rossi S, editor. Iron deficiency anaemia. In: Australian Medicines Handbook.Adelaide: Australian Medicines Handbook Pty Ltd, 2014.
11. Rossi S, editor. Iron. In: Australian Medicines Handbook. Adelaide: Australian Medicines Handbook Pty Ltd, 2014.
12. National Blood Authority Australia. Patient blood management guidelines, Available at www.blood.gov.au/pbm-guidelines [Accessed 17 April 2014].
13. Ahmad I, Gibson P. Management of Iron deficiency in patients admitted to hospital: time for a rethink of treatment principles. Int Med J 2006;36:347–54.

RESOURCES FOR PATIENTS

- Gastroenterological Society of Australia – Iron deficiency. www.gesa.org.au/consumer.asp?id=84
- BloodSafe patient resources www.sahealth.sa.gov.au/wps/wcm/connect/public+content/sa+health+internet/clinical+resources/clinical+programs/blood+products+and+programs/bloodsafe/bloodsafe+information+for+consumers/iron+therapy
- Australian Red Cross Blood Service – Iron Deficiency Anaemia. http://mytransfusion.com.au/node/iron-deficiency-anaemia

RESOURCES FOR DOCTORS

- National Blood Authority Patient Blood Management guidelines. www.blood.gov.au/pbm-guidelines
- BloodSafe eLearning Iron Deficiency Anaemia (IDA) module. www.bloodsafelearning.org.au/node/56
- BloodSafe eLearning Australia Iron Deficiency Anaemia app. www.bloodsafelearning.org.au/node/71Diagnosis and management of iron deficiency anaemia. www.mja.com.au/journal/2010/193/9/diagnosis-and-management-iron-deficiency-anaemia-clinical-updateGuidelines for the Management of Iron Deficiency Anaemia. www.bsg.org.uk/clinical-guidelines/small-bowel-nutrition/guidelines-for-the-management-of-iron-deficiency-anaemia.html
- Patient blood management The GP's guide. www.racgp.org.au/download/Documents/AFP/2013/May/201305minck.pdf
- Australian Red Cross Blood Service – patient blood management and anaemia management guidelines. www.transfusion.com.au
- Oral iron dosing chart for clinicians. www.sahealth.sa.gov.au/wps/wcm/connect/81d0f6804f7202a8b7aef774733d1f2b/OralIronDosingTreatmentAnaemia-BloodSafe-Oct2011.pdf?MOD=AJPERES&CACHEID=81d0f6804f7202a8b7aef774733d1f2b

CASE 5

LISA'S FATIGUE AND MUSCLE WEAKNESS

Lisa is 33 years of age and she presents with fatigue and muscle weakness, which have been present since the birth of her first child 7 years ago. Lisa says the weakness mainly affects her lower limbs and that she waddles when she walks. People often comment, 'Are you limping?'. Recently, she has noticed that she has difficulty holding her hairdryer when she dries her hair. Her bowels are often loose and she has stomach pains after eating.

Over the past 7 years Lisa has seen several GPs and been referred to two different neurologists. She has had many investigations but no diagnosis has been made.

Lisa looks well and has a normal colour but has mild bilateral ptosis.

You notice that Lisa sat forward during the history taking, resting her elbow on the desk and supported her chin in her cupped left hand.

No abnormality is found on further examination. Her gait is normal and there is no detectable muscle weakness.

QUESTION 1

What is the possible diagnosis?

QUESTION 2

What else should be considered in the differential diagnosis?

QUESTION 3

What would you do next?

FURTHER INFORMATION

Lisa's test results were all normal and the acetylcholine (ACh) receptor antibody (AChR-Ab) test was negative.

At Lisa's next visit you confirm mild bilateral ptosis and note that she is very quickly fatigued when holding her upper limbs in an elevated position.

You discuss the negative AChR-Ab results with her and then refer her back to the neurologist.

QUESTION 4

Does the negative serology exclude myasthenia gravis?

FURTHER INFORMATION

The neurologist ordered a muscle-specific tyrosine kinase antibody (MuSK-Ab) test and this was negative.

QUESTION 5

Are there any other investigations that would confirm myasthenia gravis in Lisa's case?

FURTHER INFORMATION

Lisa was referred for electrophysiological studies (EPS) and her single fibre electromyography (SFEMG) test result was positive.

QUESTION 6

What treatment is available for Lisa?

CASE 5 ANSWERS

ANSWER 1

Lisa presents with muscle weakness that affects her eyes and limbs. This should raise the suspicion of myasthenia gravis, which is the most common disorder of neuromuscular transmission.[1] Myasthenia gravis is an autoimmune disorder in which the ACh receptors or associated receptor proteins in the postsynaptic membrane are attacked by antibodies.[2] T-lymphocytes are also involved in the pathogenesis of myasthenia gravis.[2] Most patients with myasthenia gravis have an abnormality, either hyperplasia or thymoma, in their thymus gland.

The disease is characterised by symptoms that are often transient early in its presentation. Symptoms may remit completely for days or weeks but gradually worsen and become more persistent.

Myasthenia gravis is an uncommon disorder; it has an annual incidence of 10–20 new cases per million people[3,4] and a prevalence of 150–200 per million.[5,6] The prevalence of myasthenia gravis has been increasing over the past five decades and this increase is attributed to better recognition of the condition, an ageing population and the longer life span of affected patients.[7]

Myasthenia gravis occurs at any age but there tends to be a bimodal distribution to the age of onset with an early peak in the second and third decades (female predominance) and a late peak in the sixth to eighth decade (male predominance).[7]

Lisa's symptoms have fluctuated and affect a combination of muscle groups, which is characteristic of the condition.

ANSWER 2

As Lisa's fatigue has already been thoroughly assessed and investigated at multiple consultations and with tests involving all systems, the differential diagnosis is restricted to diseases with neurological or neuromuscular pathology. These potentially include:[8]

- thyroid eye disease (this may mimic myasthenia gravis)
- motor neuron disease
- drugs (eg penicillamine and statins have been implicated in causing a myasthenia presentation)
- thymic disease (eg thymic hyperplasia, thymoma and, rarely, thymic carcinoma)
- paraneoplasia associated with extrathymic tumours (eg small cell lung cancer and Hodgkin lymphoma)
- autoimmune disorders
- botulism, which has a rapid course and is therefore excluded.

ANSWER 3

You review Lisa and exclude all of the differential diagnoses listed above on the basis of her history and your examination findings. You confirm the presence of her ocular and limb symptoms and then discuss her situation with her most recent neurologist, who recommends testing for AChR-Ab.

You order further blood tests, including a full blood evaluation (FBE), liver function tests (LFTs), thyroid stimulating hormone (TSH), thyroid antibodies, C-reactive protein, iron studies and the test for AChR-Ab, which the neurologist recommended.

ANSWER 4

The negative ACh serology results do not exclude myasthenia gravis. It is estimated that 6–12% of patients with myasthenia gravis have negative antibody serology for both AChR-Ab and MusSK-Ab.[1] Such patients are often referred to as having seronegative myasthenia gravis and there is a suggestion that these patients may have better outcomes following treatment.[11] Seropositive myasthenia gravis occurs in 88–94% of cases.[1] Tests are for the presence of AChR-Ab and MuSK-Ab. AChR-Ab are present in 80–90% of patients with generalised myasthenia gravis[9,10] and in 40–55% of those with ocular myasthenia.[9]

ANSWER 5

Historically, the icepack test and edrophonium (tensilon) test have been used. In the ice pack test, a bag (or surgical glove) is filled with ice and placed on the closed lid for 2 minutes. The ice is then removed and the extent of ptosis is immediately assessed. The sensitivity seems to be about 80% in those with prominent ptosis. The predictive value of the test has not yet been established. This test can be used in patients with ptosis, particularly those

in whom the tensilon test is considered too risky. It is not helpful for those with extraocular muscle weakness. As it is based on the physiological principle of improving neuromuscular transmission at lower muscle temperatures, the eyelid muscles are the most easily cooled by the application of ice.[12,13]

Edrophonium chloride is an acetylcholinesterase inhibitor with a rapid onset (30–45 seconds) and short duration of action (5–10 minutes). It prolongs the presence of ACh in the neuromuscular junction and results in an immediate increase in muscle strength in many of the affected muscles. The edrophonium test should be used only in those patients with obvious ptosis or ophthalmoparesis, in whom improvement after infusion of the drug can easily be observed. The difficulty in quantifying strength independently of volition in other muscle groups makes the interpretation of the response to edrophonium too unreliable. The sensitivity of this test is in the range of 80–90% but it is associated with many false-negative and false-positive results.[9,14] Some patients with clearly established myasthenia gravis may have an equivocal or no response to edrophonium. A positive test is not specific for myasthenia gravis, as it can also occur in other conditions, such as motor neuron disease, brainstem tumors and compressive cranial neuropathies, which can present in a similar fashion.

The icepack and edrophonium tests are sensitive and easy to perform but there are concerns about high rates of false-positives with these techniques. Confirmation of a diagnosis by these tests alone is unwise.

EPS is the most important supplement to serological studies and may be used to confirm a myasthenia gravis diagnosis.[1] The two EPS tests are the repetitive nerve stimulation (RNS) and single fibre electromyography (SFEMG). The latter test is the more sensitive and is positive in >95% of those with generalised myasthenia gravis and in 85–95 % of those with ocular presentations.

ANSWER 6

In the past, myasthenia gravis was a disabling and often fatal condition, whereas today it is managed more effectively. The therapeutic approach is highly individualised and complicated and is best managed by the treating neurologist with the assistance of the GP. Variables such as the age of the patient and the severity and progression of the disease will influence treatment decisions.[15–18]

Table 1 summarises the four basic therapies used to treat myasthenia gravis. Medications used may include pyridostigmine (first-line treatment), neostigmine, prednisone, azathioprine and cyclosporine.[19,20] Other agents (ie rituximab, monthly pulse cyclophosphamide and tacrolimus) may be used in some circumstances (eg refractory myasthenia gravis).[21] Most people with myasthenia gravis will require some form of immunotherapy during the course of their illness and some people may require immunotherapy indefinitely.[21]

Table 1: Treatment options for myasthenia gravis[18–22]

Treatment option	Comments
Symptomatic treatments Acetylcholinesterase inhibitors (anticholinesterase medications)	Some patients may require no additional therapies.
Chronic immunomodulating treatments Glucocorticoids and other immunosuppressive drugs	Anticholinesterase medications may be used to reduce the dose of immunosuppressive drugs and minimise their side effects.
Rapid immunomodulating treatments Plasmapheresis and intravenous immune globulin	These agents work quickly but have a short duration of therapy. They are reserved for use in specific circumstances (eg myasthenic crisis, pre-operatively before thymectomy, when initiating slower-acting immunotherapies or as an adjuvant to other medications in patients with refractory myasthenia gravis).
Surgical treatment Thymectomy	It usually takes years for the benefits of surgery to become apparent.

CONCLUSION

Lisa was commenced on pyridostigmine, which provided a dramatic, immediate benefit. Unfortunately, this was not sustained and after 12 months she required the addition of prednisolone. Azathioprine was added later in an attempt to reduce the dose of prednisolone.

Lisa eventually had a thymectomy but, unfortunately, did not obtain any definite benefit from the procedure so she remained on pyridostigmine, prednisolone and azathioprine

In cases of myasthenia gravis, the GP is the first point of contact. Disease often evolves over time and the diagnosis may take time to emerge, causing confusion for the patient, GP and specialists along the way. In the management of such cases, there is a need to revisit the symptoms and review what could be missing.

REFERENCES

1. Bird SJ. Diagnosis of myasthenia gravis. In: Shefner JM, Targoff IN, editors. UpToDate. Waltham: Wolters Kluwer, 2014. Available at www.uptodate.com/contents/diagnosis-of-myasthenia-gravis?source=search_result&search=Diagnosis+of+Myasthenia+Gravis&selectedTitle=1%7E150[Accessed 3 April 2014].
2. Trouth AJ, Dabi A, Solieman N, Kurukumbi M, Kalyanam J. Myasthenia gravis: a review. Autoimmune Dis 2012. Available at http://dx.doi.org/10.1155/2012/874680[Accessed 3 April 2014].
3. Phillips LH. The epidemiology of myasthenia gravis. Semin Neurol 2004;24:17–20.
4. Aragonès JM, Bolíbar I, Bonfill X, et al. Myasthenia gravis: a higher than expected incidence in the elderly. Neurology 2003;60:1024.

5. Phillips LH 2nd. The epidemiology of myasthenia gravis. Ann N Y Acad Sci 2003;998:407–12.
6. Heldal AT, Owe JF, Gilhus NE, Romi F. Seropositive myasthenia gravis: a nationwide epidemiologic study. Neurology 2009;73:150.
7. Phillips LH 2nd, Torner JC, Anderson MS, Cox GM. The epidemiology of myasthenia gravis in central and western Virginia. Neurol 1992;42:1888–93.
8. Bird SJ. Differential diagnosis of myasthenia gravis. In: Shefner JM, Targoff IN, editors. UpToDate. Waltham: Wolters Kluwer, 2014. Available at www.uptodate.com/contents/diagnosis-of-myasthenia-gravis?source=search_result&search=Diagnosis+of+Myasthenia+Gravis&selectedTitle=1%7E150[Accessed 3 April 2014].
9. Meriggioli MN, Sanders DB. Myasthenia gravis: diagnosis. Semin Neurol 2004;24:31–39.
10. Chan KH, Lachance DH, Harper CM, Lennon VA. Frequency of seronegativity in adult acquired generalized myasthenia gravis. Muscle Nerve 2007;36:651–58.
11. Deymeer F, Gungor-Tuncer O, Yilmaz V, et al. Clinical comparison of anti-MUSK- vs anti-AChR-positive and seronegative myasthenia gravis. Neurol 2007;68:609–11.
12. [Sethi KD, Rivner MH, Swift TR. Ice pack test for myasthenia gravis. Neurology 1987;37:1383.
13. Golnik KC, Pena R, Lee AG, Eggenberger ER. An ice test for the diagnosis of myasthenia gravis. Ophthalmology 1999;106:1282.
14. Daroff RB. The office Tensilon test for ocular myasthenia gravis. Arch Neurol 1986;43:843.
15. Skeie GO, Apostolski S, Evoli A, et al. Guidelines for treatment of autoimmune neuromuscular transmission disorders. Eur J Neurol 2010;17:893–902.
16. Farrugia ME, Vincent A. Autoimmune mediated neuromuscular junction defects. Curr Opin Neurol 2010;23:489–95.
17. Richman DP, Agius MA. Treatment of autoimmune myasthenia gravis. Neurol 2003;61:1652–61.
18. Keesey JC. Clinical evaluation and management of myasthenia gravis. Muscle Nerve 2004;29:484–505.
19. Myasthenia gravis. In: eTG [Internet]. Melbourne: Therapeutic Guidelines Limited, 2014. Available at www.tg.org.au [Accessed 24 March 2014].
20. Rossi S, editor. Anticholinesterases in myasthenia gravis. In: Australian Medicines Handbook. Adelaide: Australian Medicines Handbook Pty Ltd, 2014. Available at www.amh.net.au/online [accessed 24 March 2014].
21. Bird SJ. Treatment of myasthenia gravis. In: Shefner JM, Targoff IN, editors. UpToDate. Waltham: Wolters Kluwer, 2014. Available at www.uptodate.com/contents/diagnosis-of-myasthenia-gravis?source=search_result&search=Diagnosis+of+Myasthenia+Gravis&selectedTitle=1%7E150 [Accessed 3 April 2014].
22. Bird SJ. Chronic immunomodulating therapies for myasthenia gravis. In: Shefner JM, Targoff IN, editors. UpToDate. Waltham: Wolters Kluwer, 2014. Available at www.uptodate.com/contents/diagnosis-of-myasthenia-gravis?source=search_result&search=Diagnosis+of+Myasthenia+Gravis&selectedTitle=1%7E150 [Accessed 3 April 2014].

RESOURCES FOR PATIENTS

- Better Health Channel. Myasthenia Gravis. Fact sheet. www.betterhealth.vic.gov.au/bhcv2/bhcarticles.nsf/pages/Myasthenia_gravis?open

Fatigue

In order to qualify for 6 Category 2 points for the QI&CPD activity associated with this unit:

- read and complete the unit of *check* in hard copy or online at the *gplearning* website at http://gplearning.racgp.org.au
- log into the *gplearning* website at http://gplearning.racgp.org.au and answer the following 10 multiple choice questions (MCQs) online
- complete the online evaluation.

If you are not an RACGP member, please contact the *gplearning* helpdesk on 1800 284 789 to register in the first instance. You will be provided with a username and password that will enable you access to the test.

The expected time to complete this activity is 3 hours.

Do not send answers to the MCQs into the *check* office. This activity can only be completed online at http://gplearning.racgp.org.au

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

FOR A FULL LIST OF ABBREVIATIONS AND ACRONYMS USED IN THESE QUESTIONS PLEASE GO TO PAGE 3.
FOR EACH QUESTION BELOW SELECT ONE OPTION ONLY.

QUESTION 1

For patients presenting with symptoms suggestive of thyroid disease, which one of the following options CORRECTLY outlines investigations required for a diagnosis of primary hypothyroidism?

A. Serum TSH
B. Serum TSH and T4
C. Serum TSH and T3
D. Serum TSH, T4 and T3
E. Serum TSH, T4 and T3 and thyroid ultrasound

QUESTION 2

The management of hypothyroidism and therapeutic treatment goals may need to be altered for certain patients depending on age and other factors. Which of the following statements regarding changes in management and goals is CORRECT?

A. Pregnant women with hypothyroidism and a history of miscarriage should cease levothyroxine treatment.
B. People with cardiovascular disease or those aged >60 years should be started on lower levels of levothyroxine.
C. Women with hypothyroidism who become pregnant do not require any change in their thyroid medication.
D. More strict treatment goals apply with advancing age.
E. None of the above is correct.

QUESTION 3

Cartier, aged 48 years, presents with a 2.5-year history of ongoing tiredness, generalised aches and pains and difficulty sleeping. She receives antidepressant therapy for depression that was diagnosed 1 year ago. She retired recently, as she could not cope with working part time. Examination reveals extensive musculoskeletal tenderness. Which of the following most CORRECTLY describes appropriate investigations for Cartier?

A. Full blood evaluation (FBE), erythrocyte sedimentation rate
B. Renal, liver and thyroid function tests
C. Vitamin D, calcium, magnesium and phosphate levels
D. Answers A, B and C
E. Answers A and B

QUESTION 4

A fibromyalgia management plan should include a combination of patient education, an exercise program, pain management, psychology and medications. Which of the following statements most CORRECTLY describes medications for fibromyalgia?

A. Amitriptyline is not useful for the management of fibromyalgia.
B. Paracetamol is not a useful adjunct therapy in fibromyalgia.
C. Milnacipran is the only medication licensed for use in fibromyalgia.
D. Duloxetine is not useful for management of fibromyalgia.
E. Non-steroidal anti-inflammatory agents are of no benefit in fibromylagia.

QUESTION 5

William is 19 years of age and presents complaining of increasing weakness and tiredness, which commenced about 1 year ago. Questioning reveals he also experiences occasional dizziness. He became a vegetarian several years ago. Examination reveals conjunctival pallor. Which of the following statements is CORRECT?

A. William should be investigated for fibromyalgia.
B. William may have iron deficiency anaemia and a FBE and iron studies are suitable first-line tests.
C. William may have a thyroid problem and a thyroid function test is a suitable first-line test.
D. William's vegetarian diet does not place him at increased risk of iron deficiency anaemia.
E. William should have an endoscopy and colonoscopy as first-line tests.

QUESTION 6

Which of the following statements regarding iron deficiency anaemia is CORRECT?

A. Serum iron is a reliable indicator of iron deficiency.
B. Hypochromic microcytic anaemia is not associated with thalassemia.

C. Reduced ferritin levels have been associated with various blood dyscrasias.

D. Hypochromic microcytic anaemia may be associated with anaemia of chronic disease.

E. Iron supplements must be taken on an empty stomach.

QUESTION 7

Which of the following options most CORRECTLY outlines investigations for fatigue recommended by guidelines where chronic fatigue syndrome is suspected?

A. FBE, erythrocyte sedimentation rate, C-reactive protein, serum ferritin

B. FBE, C-reactive protein, serum ferritin

C. FBE, erythrocyte sedimentation rate, serum ferritin (children and young people only)

D. Answers A and B

E. Answer B only

QUESTION 8

Julianne is an optometry student aged 20 years and has a history of viral infections and fatigue. She has put her university studies on hold, as she was not able to cope with the daily commute and the workload required by her course. She was recently diagnosed with chronic fatigue syndrome (CFS)/myalgic encephalomyelititis. Which of the following statements regarding her diagnosis and potential management is the most CORRECT?

A. Most diagnoses of CFS occur in people aged 20–40 years.

B. Guidelines state that a diagnosis of CFS can be made in an adult when other possible causes of excessive fatigue have been excluded and symptoms have persisted for more than 3 months.

C. A trial of complementary therapies and supplements (eg vitamin B_{12}, vitamin C, co-enzyme Q10, magnesium, multivitamins or minerals) is warranted, as these agents improve symptoms.

D. Medications such as monamine oxidase inhibitors, glucocorticoids (such as hydrocortisone), mineralocorticoids (such as fludrocortisone), dexamphetamine, methylphenidate, thyroxine and antiviral agents may be useful for people with CFS.

E. The only medication that has been approved for use in people with CFS is milnacipran.

QUESTION 9

Myasthenia gravis is a rare condition but the GP most often is the first point of contact for patients. Which of the following statements is CORRECT?

A. Myasthenia gravis occurs mainly in people aged >70 years.

B. Negative AChR-Ab serology excludes a diagnosis of myasthenia gravis.

C. Negative MuSK-Ab serology excludes a diagnosis of myasthenia gravis.

D. Most people with myasthenia gravis have an abnormality with their thyroid gland.

E. The prevalence of myasthenia gravis has risen in recent decades due to better recognition of the condition, an ageing population and the longer life span of affected patients.

QUESTION 10

Pria is 39 years of age and was recently diagnosed with myasthenia gravis following a 5-year history of increasing fatigue and muscle weakness of her eyes and limbs, eventually resulting in minor ptosis of her right eye and pronounced ptosis in her left eye. Which of the following is CORRECT with regards to current treatment options for myasthenia gravis?

A. There are no known pharmacological treatment options for myasthenia gravis.

B. The benefits of thyroid surgery for myasthenia gravis may take years to become apparent.

C. Plasmapherisis is of no benefit for people with myasthenia gravis.

D. Most people with myasthenia gravis will require immunotherapy indefinitely.

E. Management of myasthenia gravis is highly individualised and complicated and should be managed by a neurologist with GP assistance.

check

Independent learning program for GPs