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MEDICAL PROGRESS

April 2012 VOL. 39 NO. 4

In Focus:

Ophthalmology

MEDICAL PROGRESS

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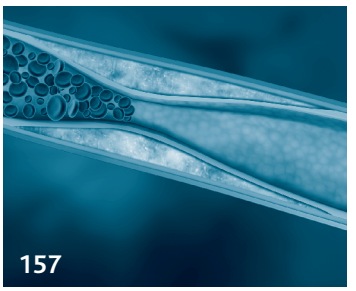

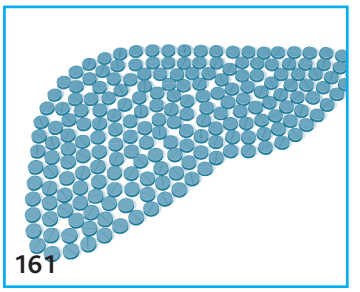

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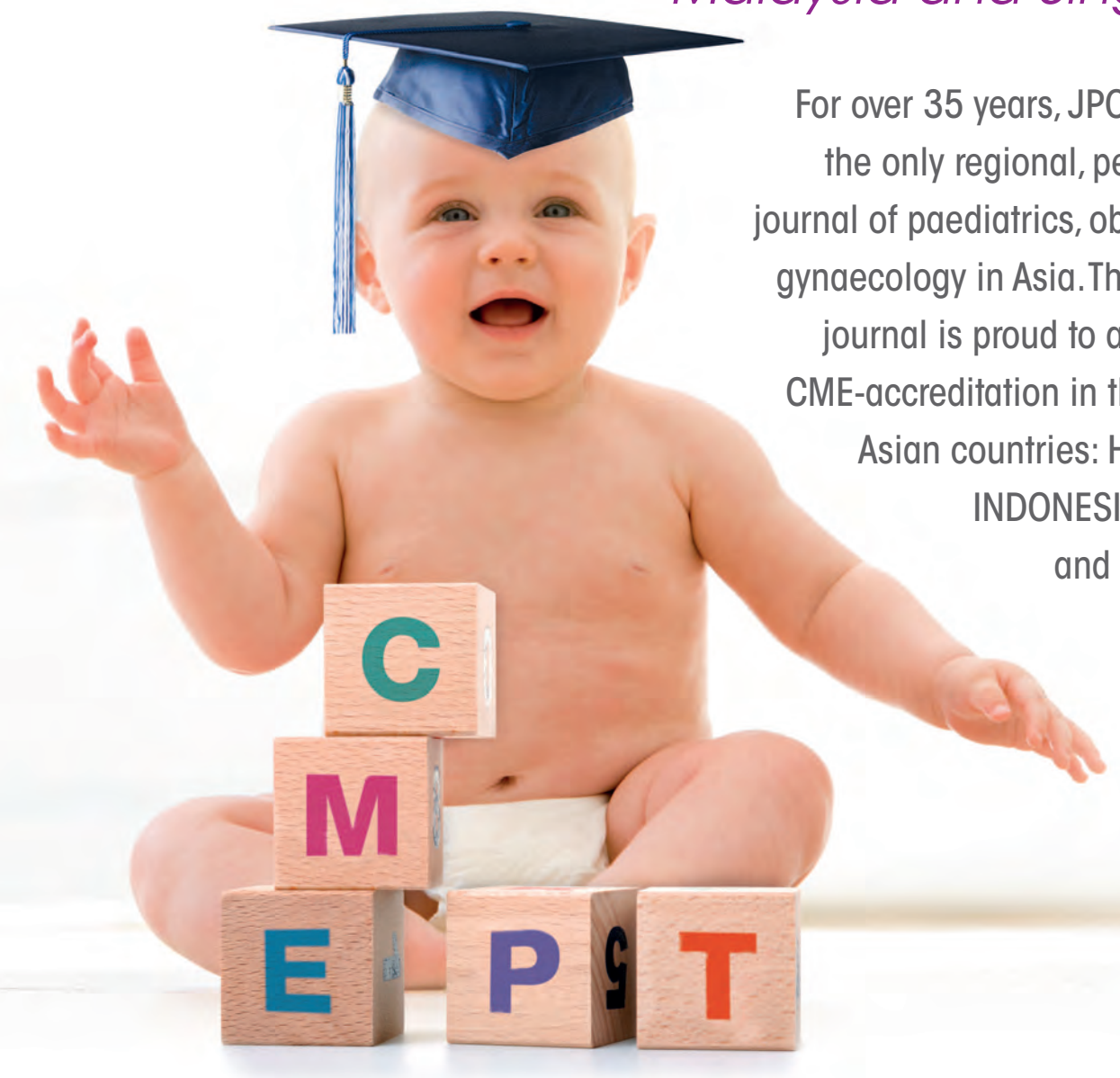

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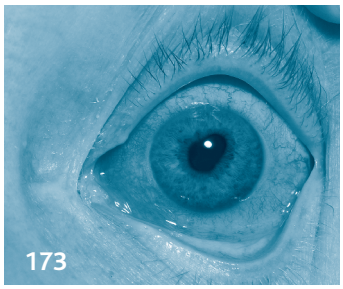

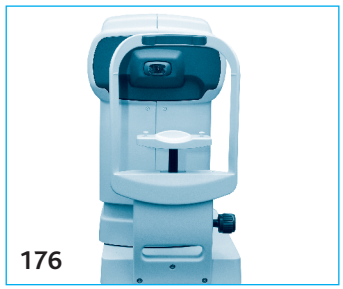

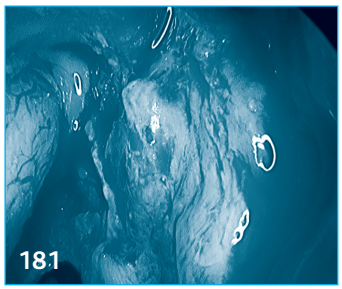

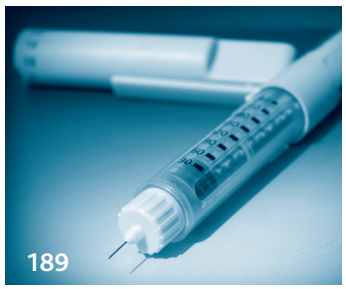

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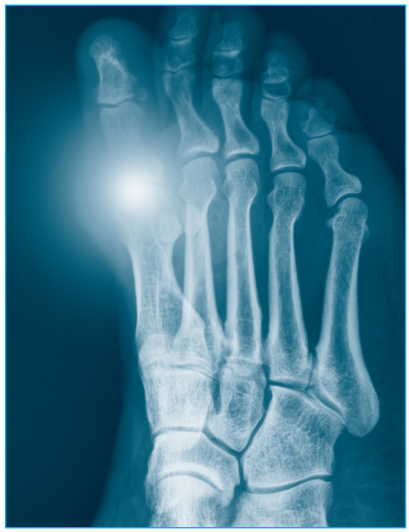

◆ In Focus ◆

Gout

- **Addressing Problems in Gout and Hyperuricemia**
- **When It Isn't Gout**

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The source of the infant formula product is of cow's milk origin.

Refer to:
1. Code of Ethics for the Marketing of Infant Foods and Related Products, 4th edition, Ministry of Health Malaysia, August 2008.
2. International Code of Marketing of Breast Milk Substitutes, adopted by the World Health Assembly in Resolution WHA 34.22, May 1981.

References:
1. Wahn U, Chuchalin A, Kowalski ML. *Chem Immunol Allergy (Karger, Basel)* 2004; 84: 128-134. 2. Exl BM & Fritsche R. Cow's milk protein allergy and possible means for its prevention. *Nutrition* 2001; 17(7/8): 642-51. 3. Hayes T, Wood RA. *Arch Pediatr Adolesc Med* 2005; 159: 810-816. 4. von Berg A, Filipiak-Pittroff B, Krämer U *et al*, for the GINIplus Study Group. *J Allergy Clin Immunol* 2008; 121: 1442-1447. 5. Baumgartner M, Brown CA, Secretin MC et al. *Nutr Res* 1998; 18: 1425-1442. 6. Osborn DA, Sinn J. *Cochrane Database Syst Rev* 2006; 4: CD003664. 7. Kalliomäki M, Salminen S, Arvilommi H *et al*. *Lancet* 2001; 357: 1076-1079. 8. Kalliomäki M, Salminen S, Poussa T *et al*. *Lancet* 2003; 361: 1869-1871.

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References:

1. Gronlund MM, Lehtonen OP, Eerola E, Kero P. *J Pediatr Gastroenterol Nutr* 1999; 28: 19-25. 2. Penders J, Thijs C, Vink C *et al. Pediatrics* 2006; 118: 511-21. 3. Saavedra JM. *Nutr Clin Pract* 2007; 22: 351-365. 4. Walker WA. *J Pediatr Gastroenterol Nutr* 2000; 30 (Suppl. 2): S2-S7. 5. Gronlund MM, Arvilommi H, Kero P *et al. Arch Dis Child Fetal Neonatal Ed* 2000; 83: F186-F192. 6. Thilaganathan B, Meher-Homji N. Nicolaides KH. *Am J Obstet Gynecol* 1994; 171: 1271-1272. 7. Langhendries JP, Detry J, Van Hees J *et al. J Pediatr Gastroenterol Nutr* 1995; 21: 177-81. 8. Mohan R, Koebnick C, Schildt J *et al. J Clin Microbiol* 2006; 44(11): 4025-4031. 9. Saavedra JM. Bauman NA, Oung I *et al. Lancet* 1994; 344: 1046-1049. 10. Chouraqui JP, Van Egroo L-D, Fichot M-C. *J Pediatr Gastroenterol Nutr* 2004; 38: 288-292.

Product Symbol: NWB023/LEB032/LEB047/LNFB003
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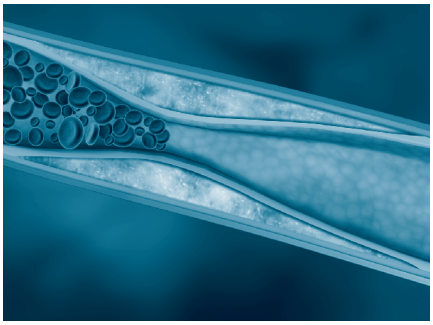
CARDIOLOGY

Statins and coronary disease regression



Statin therapy may slow the progression of coronary atherosclerosis or even reverse it. The effects of atorvastatin and rosuvastatin have been compared in a large international trial.

A total of 1,039 patients with coronary disease were randomized at 208 centres to atorvastatin 80 mg daily or rosuvastatin 40 mg daily for 104 weeks. Intravascular ultrasonography was performed at baseline and at 104 weeks. At the end of the trial, low-density lipoprotein (LDL) cholesterol levels were significantly lower in the rosuvastatin group than in the atorvastatin group (1.62 vs 1.82 mmol/L). The rosuvastatin group also had significantly higher levels of high-density lipoprotein (HDL) cholesterol (1.30 vs 1.26 mmol/L). The percent atheroma volume decreased by 1.22% (rosuvastatin) vs 0.99% (atorvastatin), a non-significant difference. The normalized total atheroma volume decreased by 6.39 mm^3 (rosuvastatin) vs 4.42 mm^3 (atorvastatin), a significant difference. Regression of atheroma occurred in most patients in each group, and the drugs were well tolerated.

Rosuvastatin lowered LDL cholesterol levels and increased HDL cholesterol levels to a greater extent than atorvastatin, but their effects on atheroma regression were similar

Nicholls SJ et al. Effect of two intensive statin regimens on progression of coronary disease. NEJM 2011; 365: 2078–2087.

Biodegradable vs durable polymer stents

Drug-eluting stents, compared with bare metal stents, reduce the risk of repeat revascularization but may increase the risk of very late (> 1 year) stent thrombosis. It has been suggested that this increase in risk may arise from the durable nature of the polymer used in their construction that allows polymer material to persist and stimulate an inflammatory response. Drug-eluting stents made of biodegradable polymer might avoid this risk. A multinational European trial has shown that biodegradable polymer drug-eluting stents may have an advantage over durable polymer stents.

A total of 1,707 patients with coronary disease (2,472 lesions) were randomized to biodegradable polymer biolimus-eluting stents (BPBES) or durable polymer sirolimus-eluting stents (DPSES). After 4 years of follow-up, BPBES were non-inferior to DPSES. The primary end point (myocardial infarction, clinically indicated target vessel revascularization, or cardiac death) occurred in 18.7% (BPBES) vs 22.6% (DPSES) of the patients, a 19% difference proving the non-inferiority of BPBES. There was a 38% overall reduction in stent thrombosis, a significant 80% reduction between years 1 and 4 and a non-significant 0.01% reduction during the first year. There was no significant reduction in primary end point events associated with stent thrombosis during the first year but a significant 83% reduction in such events between years 1 and 4.

BPBES were non-inferior to DPSES and reduced the risk of very late stent thrombosis. It is not known whether BPBES will prove to be better than second-generation drug-eluting stents.

Stefanini GG et al. Long-term clinical outcomes of biodegradable polymer biolimus-eluting stents versus durable polymer sirolimus-eluting stents in patients with coronary artery disease (LEADERS): 4-year follow-up of a randomised non-inferiority trial. Lancet 2011; 378: 1940–1948; Waksman R, Maluenda G. Polymer drug-eluting stents: is the future biodegradable? Ibid: 1900–1902 (comment).

Eleven-year follow-up of patients in statin trial

The short-term benefits of statin treatment for cardiovascular at-risk patients are well established, but there are concerns about possible long-term problems such as increased cancer risk. Now, a long-term follow-up report of one trial has shown no evidence of such risks.

In the Medical Research Council and British Heart Foundation Heart Protection Study, 20,536 patients at high cardiovascular risk were randomized to simvastatin 40 mg daily or placebo. Mean follow-up in the trial was 5.3 years, but post-trial follow-up extended mean overall follow-up to 11.0 years. In-trial follow-up showed an average reduction in low-density lipoprotein cholesterol level of 1.0 mmol/L and a 23% reduction in major vascular events. During post-trial follow-up, statin use and serum lipid levels were similar in the two groups, and there were no further reductions in major vascular event rates. During the 11 years of total follow-up, the rates of cancer incidence and mortality and of non-vascular mortality were similar in the two groups.

Statin treatment is effective, and no long-term adverse effects emerged in this study. In particular, there was no increase in cancer. *Lancet* commentators conclude that concerns about the long-term safety of statin treatment for at-risk patients should be 'put to rest'.

Heart Protection Study Collaborative Group. Effects on 11-year mortality and morbidity of lowering LDL cholesterol with simvastatin for about 5 years in 20,536 high-risk individuals: a randomised controlled trial. Lancet 2011; 378: 2013–2020; Kohli P, Cannon CP. Statins and safety: can we finally be reassured? Ibid: 1980–1981 (comment).

GENERAL MEDICINE

Low-dose interleukin-2 for HCV-induced vasculitis

Cryoglobulinaemia is common in chronic hepatitis C virus (HCV) infection, and some patients develop cryoglobulinaemic

vasculitis (mixed cryoglobulinaemia). In patients with vasculitis, there is a deficiency of regulatory T cells (Treg cells). Stimulation of Treg-cell production with interleukin 2 might therefore be effective therapy for HCV-associated vasculitis. A trial in France has given support to this hypothesis.

In an open-label, prospective, phase I/IIa study, 10 patients with HCV-associated vasculitis non-responsive to antiviral therapy, rituximab, or both, were given interleukin 2 (1.5 million IU daily for 5 days, then 5 days of 3.0 million IU daily at weeks, 3, 6, and 9. There were no serious adverse events. Effector T-cell activation was not induced, there were no flares of vasculitis, and HCV viraemia did not increase. Cryoglobulinaemia was reduced in nine of the 10 patients, and the vasculitis improved in eight. After treatment with interleukin 2, blood mononuclear cell studies showed a global attenuation of the signatures for inflammation and oxidative stress mediators. There was marked Treg-cell recovery.

Low-dose interleukin-2 therapy was associated with clinical improvement in HCV-associated vasculitis.

Saadoon D et al. Regulatory T-cell responses to low-dose interleukin-2 in HCV-induced vasculitis. NEJM 2011; 365: 2067–2077; Bluestone JA. The Yin and Yang of interleukin-2-mediated immunotherapy. Ibid: 2129–2131 (editorial).

Thromboprophylaxis for acutely ill medical inpatients

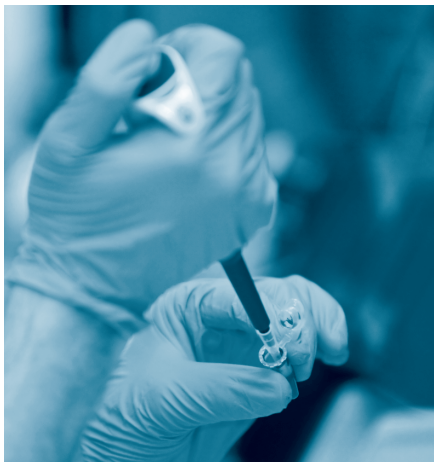
Drug prophylaxis against venous thromboembolism (VTE) is effective in both surgical patients and acutely ill medical inpatients. Extended prophylaxis (continuing after hospital discharge) has resulted in lower rates of VTE but higher risk of bleeding among acutely medically ill patients. Now, 30 days of apixaban (an oral direct inhibitor of activated factor X) has been compared with 6–14 days of subcutaneous enoxaparin for thromboprophylaxis in such patients.

A total of 6,528 patients aged 40–101 (mean, 67 years) with congestive heart failure, respiratory failure, or other medical disorders were randomized to oral apixaban 2.5 mg twice daily for 30 days or subcutaneous enoxaparin for the duration of their hospital stay (6–14 days). The primary efficacy outcome (death from VTE, pulmonary embolism, or symptomatic deep vein thrombosis within 30 days) was evaluated in 4,495 patients and was reached by 2.7% (epixaban) vs 3.1% (enoxaparin), a non-significant difference. Major bleeding had occurred by 30 days in 0.47% vs 0.19%, a significant 2.6-fold increase in risk with apixaban.

Apixaban for 30 days was not superior to enoxaparin for 6–14 days (duration of hospital stay) for thromboprophylaxis in acutely ill medical inpatients and was associated with greater risk of major bleeding.

Goldhaber SZ et al. Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients. NEJM 2011; 365: 2167–2177.

Bioartificial stem-cell tracheobronchial transplant



Most patients with primary tracheal cancers have inoperable tumours at presentation. Workers in Stockholm, Sweden, have reported providing a bioartificial transplant.

A 36-year-old man had recurrent primary cancer of the distal trachea and main bronchi. His treatment consisted of complete tumour resection and replacement of the airway using a tailored bioartificial nanocomposite previously seeded with autologous bone marrow mononuclear cells via a bioreactor for 36 hours. He was given subcutaneous granulocyte colony-stimulating factor and epoetin on the day before the operation and on alternate days for 2 weeks afterwards. He was without symptoms and free of tumour 5 months after operation. The transplant was functional and partly covered by epithelium, and markers of healing and growth potential were favourable.

In this patient, tracheobronchial transplantation with a stem cell-seeded bioartificial nanocomposite seems to have been successful. Bioartificial organ transplantation is in its infancy, and more research and long-term follow-up studies are needed.

Jungebluth P et al. Tracheobronchial transplantation with a stem-cell-seeded bioartificial nanocomposite: a proof-of-concept study. Lancet 2011; 378: 1997–2004; Ott HC, Mathisen DJ. Bioartificial tissues and organs: are we ready to translate: Ibid: 1977–1978 (comment).

Statins and infections: No benefit

Observational studies have suggested that people on statins might be less prone to infection. Now, a systematic review and meta-analysis of 11 trials has shown no protective effect of statins against infection.

The 11 trials included 30,947 patients receiving a statin or placebo. Infection was reported in 2,368 subjects on statins and 2,287 on placebo. Meta-analysis showed that statin treatment did not affect the risk of infection or death related to infection.

Randomized controlled trials of statin therapy vs placebo have shown no evidence that statin therapy increases the risk of infection, but not all trials provided this information.

Van den Hoek HL et al. Statins and prevention of infections: systematic review and meta-analysis of data from large randomised placebo controlled trials. BMJ 2011; 343: 1242 (d7281); Golomb BA. Do statins reduce the risk of infection? Ibid: 1235 (d7134).

NEUROLOGY

Cortical demyelinating lesions in early multiple sclerosis

Cortical lesions in multiple sclerosis (MS) are associated with cognitive deterioration and disease progression. They are of three types: lesions extending into the cortex from the white matter (leukocortical), lesions extending radially from cortical microvessels (intracortical), and lesions extending into the cortex from the pia mater (subpial). A neuropathological study of 138 patients has been reported.

Each of the patients had had a brain biopsy, and cortical tissue was obtained in passing during biopsy of white matter lesions. Most had been suspected of having a tumour, and biopsy had been done stereoscopically within days or weeks of presentation. Cortical demyelination was found in 53 patients (38% of the total), and 25 of these (47%) had definite MS. Of the 85 patients without cortical demyelination, 33 (39%) had definite MS. $CD3^+$ T-cell infiltrates were present in 82% of examined lesions and macrophage-associated demyelination in 41%. Among patients with enough meningeal tissue to study, meningeal inflammation was found adjacent to cortical demyelination.

Among patients with early MS, cortical demyelinating lesions were frequent, inflammatory, and strongly associated with meningeal inflammation. Cortical neuronal loss may be directly associated with inflammatory demyelination, and suppression of this inflammation could be neuroprotective in both grey and white matter.

Lucchinetti CF et al. Inflammatory cortical demyelination in early multiple sclerosis. NEJM 2011; 365: 2188–2197; Calabresi PS. Inflammation in multiple sclerosis – sorting out the gray matter. Ibid: 2231–2233 (editorial).

EEG to detect awareness in vegetative state patients

When assessed in detail, up to 43% of patients with a diagnosis of vegetative state show some signs of consciousness. Use of

functional magnetic resonance imaging may demonstrate awareness, but it is not generally available. Now, a study at two hospitals, in England and Belgium, has shown that an electroencephalography (EEG)-based assessment might demonstrate ability to understand commands.

The study included a total of 16 patients with a clinical diagnosis of vegetative state (Coma Recovery Scale-Revised definition) and 12 healthy controls. EEG recordings showed reductions in power of μ and β frequency bands over the appropriate areas of the motor cortex on imagining movements of body parts. Sometimes, there were increases in contralateral areas of the motor cortex or surrounding the reduced-power areas. Subjects were asked to respond to a beep by imagining making a tight fist with their right hand on four to eight occasions and by imagining wiggling the toes on both feet on four to eight other occasions. Controls were asked to listen to the task but not to follow it. Appropriate responses were detected by EEG in three of the 16 patients. Two of five post-traumatic patients and one of 11 patients with non-traumatic brain injury responded.

These EEG techniques might be a useful, readily available bedside method for detecting awareness in patients in an apparently vegetative state. *Lancet* commentators discuss the implications of these findings and conclude that they demonstrate 'something different than (sic) the presence and absence of consciousness'.

Cruse D et al. Bedside detection of awareness in the vegetative state: a cohort study. Lancet 2011; 378: 2088–2094; Overgaard M, Overgaard R. Measurements of consciousness in the vegetative state. Ibid: 2052–2054 (comment).

ONCOLOGY

Advanced renal cell carcinoma: Axitinib vs sorafenib

Renal cell carcinoma often presents at an advanced stage, and many patients who have localized disease at presentation later relapse. Increased angiogenesis is a feature of these tumours, and effective anti-angiogenic agents include sunitinib, sorafenib, pazopanib, and bevacizumab. Axitinib is a highly potent, selective, second-generation inhibitor of vascular endothelial growth factor receptor (VEGFR) 1, 2, and 3. In a randomized controlled trial at 175 centres in 22 countries, axitinib has been compared with the first-generation VEGFR inhibitor, sorafenib, for the treatment of advanced renal cell carcinoma.

The trial included 723 patients with progressive renal cell carcinoma, despite treatment with sunitinib, bevacizumab plus interferon-alfa, temsirolimus, or cytokines. Randomization was to axitinib 5 mg twice daily (increasing to 7 mg or 10 mg in selected patients) or sorafenib 400 mg twice daily. The median progression free survival was 6.7 months (axitinib) vs 4.7 months (sorafenib), a highly significant difference. The rates of discontinuation because of adverse effects were 4% vs 8%. The most common adverse events were diarrhoea, hypertension, and fatigue with axitinib, and diarrhoea, palmar-plantar erythrodysaesthesia, and alopecia with sorafenib.

Axitinib prolonged progression-free survival compared with sorafenib. The optimum first- and second-line treatments for advanced renal cell carcinoma have yet to be established.

Rini BI et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. Lancet 2011; 378: 1931–1939; Bex A, Haanen J. Tilting the AXIS towards therapeutic limits in renal cancer. Ibid: 1898–1900 (comment).

Aspirin to prevent colorectal cancer in Lynch syndrome

Prophylactic aspirin may prevent the development of colorectal adenomas. Now, an international trial has shown that daily aspirin reduced the risk of colorectal cancer in patients with Lynch syndrome (hereditary non-polyposis colon cancer).

A total of 861 patients (carriers of Lynch syndrome) were randomized in a two-by-two factorial design trial to aspirin or placebo and to resistant starch or resistant starch placebo. Only the results of the aspirin trial are reported. After a mean follow-up of 55.7 months, 18 of 427 patients on aspirin and 30 of 434 on placebo had developed colorectal cancer, a non-significant 37% reduction with aspirin compared with placebo. Further statistical analysis gave a significant reduction in incidence of 44%. Among patients who were treated for at least 2 years, per-protocol analysis showed a significant 59% reduction in risk and a highly significant incidence rate ratio of 0.37. The adverse event rates during the intervention were similar in the two groups.

Aspirin 600 mg daily taken by carriers of hereditary colorectal cancer reduced the cancer incidence.

Burn J et al. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. Lancet 2011; 378: 2081–2087; Chan AT, Lippman SM. Aspirin and colorectal cancer prevention in Lynch syndrome. Ibid: 2051–2052 (comment).

Treatment of advanced neuroendocrine tumours associated with carcinoid syndrome

The 5-year mortality in patients with neuroendocrine (carcinoid) tumours is around 65%; nearly 50% of patients have metastatic disease. The prognosis is better for patients with well-differentiated tumours—locoregional rather than distant spread—and primary tumours in the jejunum, ileum, or caecum rather than lung or colon. There are no approved anti-tumour drugs for the treatment of progressive gastrointestinal or lung neuroendocrine tumours. Somatostatin analogues such as octreotide or lanreotide treat the hormone-related symptoms of carcinoid syndrome, and octreotide long-acting repeatable (LAR) also has anti-tumour activity. Overactivation of the cell regulatory kinase, mammalian target of rapamycin (mTOR), is involved in the development of neuroendocrine tumours, and everolimus, an inhibitor of mTOR, increased progression-free survival in patients with advanced pancreatic neuroendocrine tumours. Now, a study in Australia, Europe, and the USA has shown improved results with a combination of everolimus plus octreotide LAR for patients with neuroendocrine tumours.

A total of 429 patients aged 18 years or older with progressive, low- or intermediate-grade, locally advanced or metastatic neuroendocrine tumours and carcinoid syndrome were randomized to intramuscular octreotide LAR 30 mg every 28 days plus either oral everolimus 10 mg daily or placebo. Only 71 patients completed the trial, but 426 received their allocated treatment. Median progression-free survival was 16.4 months (everolimus) vs 11.3 months (placebo), a significant difference. Adverse reactions were mostly grade 1 or 2, and stomatitis, rash, fatigue, and diarrhoea were more common in the everolimus group.

The addition of everolimus to treatment with octreotide LAR prolonged progression-free survival.

Pavel ME et al. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. Lancet 2011; 378: 2005–2012; Rindi G, Caplin M. mTOR inhibitor therapy for patients with carcinoid. Ibid: 1978–1980 (comment).

SURGERY

Effect of different materials for new hips

There have been concerns about the effectiveness of metal-on-metal hip implants compared with implants made of other materials. A systematic review has suggested that metal-on-metal implants may lead to a greater need for revision operation.

The review included 18 comparative studies with 3,139 patients (3,404 hips) and over 830,000 operations in national registries. In the trials, the results as regards functional outcomes and quality of life were similar in patients with traditional polyethylene-based hip implants and those with newer (metal on metal or ceramic on ceramic) implants. In a pooled analysis of four studies, there was a suggestion of better results at 2 years with metal-on-polythene compared with metal-on metal implants. Data from over 720,000 patients in the three largest registries (Australia, New Zealand, and England and Wales) showed a greater risk of revision surgery after metal-on-metal compared with metal-on-polythene hip implants.

Metal-on-metal hip implants may be associated with a greater need for revision surgery.

Sedrakyan A et al. Comparative assessment of implantable hip devices with different bearing surfaces: systematic appraisal of evidence. BMJ 2011; 343: 1189 (d7434); Fary C et al. Diagnosing and investigating adverse reactions in metal on metal hip implants. Ibid: 1218–1222 (d7441) (Practice).

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*MRNI = Malaysian Recommended Nutrient Intakes

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References:
1. Wyeth Nutrition website. Available at: [illegible] Accessed on November 22,2010.
2. Recommended Nutrient Intakes Malaysia 2005. Available at: [illegible] Accessed on Nov 30 2010. 3. Russell RM, et al. J Nutr 1999;129:751-753. 4. Weimann A, et al. Clin Nutr 2006;25:224-244.

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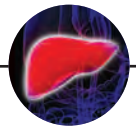
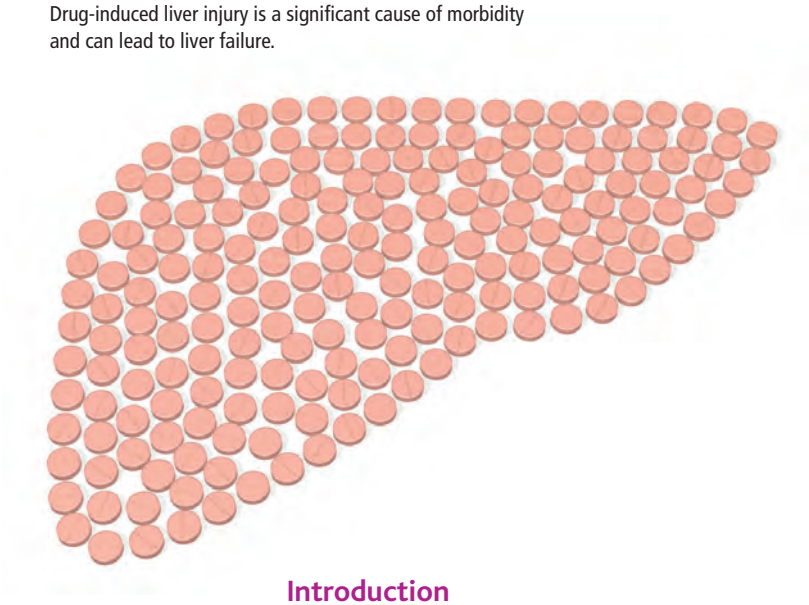


Drug-induced Liver Injury: What Would a Liver Doctor Do?

Geoffrey C Farrell, MD, FRACP; Shivakumar Chitturi, MD, FRACP

Drug-induced liver injury is a significant cause of morbidity. Practical management strategies for suspected drug-induced liver injury, including useful investigations and appropriate referral, are proposed in this case-based article.

Drug-induced liver injury is a significant cause of morbidity and can lead to liver failure.



Introduction

Drug-induced liver injury (DILI) is a significant cause of morbidity, and GPs are usually the first point of contact for affected individuals. This article provides an overview of the general practice management of patients with DILI, using four cases to illustrate various scenarios. Consider the following cases before reading the commentaries on each.

Case Scenarios

Case 1

LB, a 52-year-old woman with recurrent depression and type 2 diabetes, was hypertensive (blood pressure [BP] 155/95 mm Hg) 8 weeks ago and started taking enalapril 10 mg daily. She has also been taking carbamazepine, fluoxetine, metformin, tolbutamide and fluvastatin for at least 18 months. She now presents with 3 days of fever, anorexia, nausea and dark urine. Dipstick urine test confirms bilirubinuria and a rash is noted, similar to that illustrated for a different patient in Figure 1.

What would you do?

Case 2

You have been called to a nursing home to see MG, a 74-year-old woman who was noticed by her relatives 2 days ago to be jaundiced. She has early dementia and severe osteoarthritis of both knees and hips. In the preceding 2 months, she had rejected food and had lost 5 kg in weight. Your colleague ordered an ultrasound, hepatitis serology and liver biochemistry. The ultrasound was normal, and the hepatology serology was all negative. The other results were as follows: serum bilirubin, 80 mmol/L (upper limit of normal [ULN], < 20 mmol/L); alanine transaminase (ALT), 3,000 U/L (ULN, < 40 U/L), aspartate transaminase (AST),

4,000 U/L (ULN, < 40 U/L); albumin, 38 g/L (normal range, 35–53 g/L); international normalized ratio (INR), 2.5 (ULN, < 1.3).

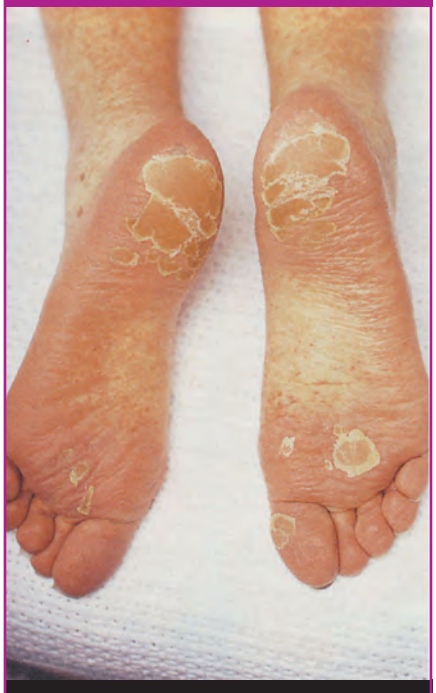
What would you do?

Case 3

BO is a 64-year-old Indian man with a history of type 2 diabetes, two myocardial infarctions and placement of three coronary artery stents. Apart from his waist circumference of 99 cm, you notice that hypercholesterolaemia is the only uncontrolled risk factor (total cholesterol, 6.8 mmol/L; high-density lipoprotein [HDL] cholesterol, 0.7 mmol/L [ideally greater than 1.2 mmol/L]; low-density lipoprotein [LDL] cholesterol, 6.1 mmol/L [ideally less than 3.0 mmol/L]). However, Mr O has been told that he cannot take statins because he has liver dysfunction (ALT, 150 U/L; γ-glutamyltransferase (GGT), 75 U/L (ULN, < 35 U/L).

Is it appropriate to prescribe a statin?

Figure 1.



Desquamating erythematous rash of the feet and ankles, with punctuated erythematous or purpuric lesions (which were palpable). The patient, who started taking allopurinol 6 weeks earlier, has drug-induced liver injury (granulomatous hepatitis) and interstitial nephritis with vasculitis.

Case 4

JL is a 45-year-old male taxi driver with psoriatic arthritis and moderately severe psoriasis of the scalp, arms and trunk. He was treated with methotrexate (15 mg once a week) for 7 years (total about 5 g) with excellent control. This patient found information on the internet that methotrexate could cause cirrhosis (of which his father died); he therefore stopped taking methotrexate about 18 months ago. His hands are now so painful and stiff that he cannot drive, and he is therefore unemployed.

Can you safely prescribe methotrexate again?

What Would a Liver Doctor Recommend for General Practice Management?

Case 1

LB has symptoms of acute hepatitis, bilirubinuria being consistent with this, together with fever and rash, within 8 weeks of starting a new medication. GPs should first exclude other causes of acute hepatitis and jaundice, for example, by hepatitis serology and hepatobiliary ultrasonography before considering drug-induced liver disease.

Prominent anorexia is more in favour of hepatitis than biliary obstruction from, for example, gallstones and pancreatic cancer. However, neither fever nor rash is a usual feature of viral hepatitis. The presence of fever, rash and even relatively non-specific gastrointestinal symptoms in someone taking a new medication strongly suggest a drug reaction. In this case, the hepatitis symptoms and bilirubinuria make a hepatic drug reaction (or 'drug hepatitis') likely.

Diagnostic Tests

Liver function tests (LFTs) will confirm a form of acute liver injury. With the clustering of LB's clinical features, there may be a raised serum bilirubin level and substantial elevation of levels of ALT (fivefold or more above upper limit of normal) and/or serum alkaline phosphatase (SAP; to greater than twice the upper limit of normal) but with relatively normal levels of serum albumin and globulins.

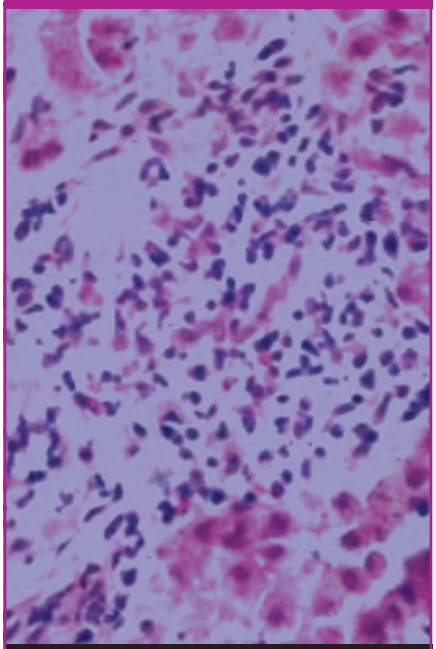
Two other features of the biochemistry may be helpful. First, concomitantly major elevations of ALT and SAP, or a 'mixed picture', is particularly common with hepatic drug reactions, and this is why the less committal term 'drug-induced liver injury' is now often used. Second, abnormalities of INR (or prothrombin time) reflect severely impaired liver function and commonly occur with severe forms of DILI, such as that caused by isoniazid. Together with the clinical features of jaundice, repeated vomiting or clouding of consciousness and/or confusion, a prolonged INR indicates incipient liver failure; such patients need urgent and immediate referral to a major hospital or a liver transplant centre.

Causative Agents

Generally, the agent started most recently, particularly when it has previously been implicated in DILI, is the most likely culprit. Typically, the onset of drug hepatitis is between 2 and 12 weeks after starting exposure, rarely after 12 months.

LB's case is illustrative, the drug she started most recently being enalapril. Angiotensin-converting enzyme (ACE) inhibitors have been associated with cholestatic hepatitis (Figure 2) and

Figure 2.



Liver biopsy taken from a patient with a similar history to that of LB (Case 1). This patient had been taking enalapril for 6 weeks as treatment for hypertension. In addition to liver cell injury and parenchymal inflammation (hepatitis), there is portal tract inflammation (including both neutrophils and eosinophils) with bile duct injury.

other forms of DILI.

ACE inhibitors and other antihypertensive agents are individually rare causes of DILI (less than 1 per 10,000 persons exposed), but so too are most other drugs. Among more than 300 agents implicated as possible causes of DILI, few are associated with a frequency of drug reactions greater than 0.1%. The agents most often implicated come from the most commonly used groups of drugs, such as antimicrobials (amoxycillin–clavulanate being most often implicated), non-steroidal anti-inflammatory drugs (NSAIDs) and anticancer drugs. However, agents from every category, including herbal and other complementary medicines, have been associated with rare instances of DILI.[1] A list of potentially hepatotoxic drugs is provided in the Table.

In LB's case, carbamazepine is a well-known cause of DILI, but the fact that she has been taking it for longer than 18 months makes it a highly unlikely cause of her present symptoms.

Management

Diagnosis is the key to management of DILI. Cases not recognized as instances of DILI carry a bad prognosis because continued drug ingestion after onset of liver injury is a critical factor for poor prognosis, as has been well documented for isoniazid.[2] Other prognostic factors include jaundice, particular agents (halothane, mitochondrial toxins such as the older highly active antiretroviral therapy [HAART] agents, and terbinafine), polypharmacy, advanced age and co-morbidities.

If LB stops her ACE inhibitor (it can be replaced with a different antihypertensive), rapid recovery (within 1 to 2 weeks) would be anticipated. Corticosteroids are not helpful for DILI. Referral is advised if there are adverse laboratory findings or when the clinical course is atypical or prolonged as patients may need a liver biopsy to confirm the diagnosis (Figure 2).

Case 2

MG's extreme elevation of transaminases suggests severe acute liver injury. The pattern of very high elevations of transaminases is found only with hepatic necrosis, ischaemia-reperfusion injury (usually due to acute cardiac failure or other cause of profound hypotension or hypoxia) and DILI (specifically that caused by paracetamol). Higher levels of AST relative to ALT often accompany paracetamol hepatotoxicity, and this is attributable to mitochondrial injury.

This patient's high serum bilirubin and INR prolongation indicate poor liver function and an uncertain prognosis; there may also be impaired renal function. Her higher levels of AST relative to ALT are suggestive of paracetamol hepatotoxicity.

Dose-dependent Hepatotoxicity

Although paracetamol is a dose-dependent hepatotoxin, it is important to understand that the difference between a safe dose and a hazardous dose can vary markedly between individuals. First, there is a difference between short-term (a day or two) and more prolonged dosing (several days). Second, a number of host factors modify paracetamol metabolism and therefore the risk of liver injury, by favouring an increased proportion of the drug being oxidized by the cytochrome P450 (CYP)2E1 pathway.

CYP2E1 is induced by alcohol consumption and fasting, which also deplete stores of hepatic glutathione, the antioxidant that protects tissues against oxidative injury. The increased susceptibility of alcohol abusers to paracetamol hepatotoxicity (even at doses not usually regarded as toxic) is well known for these reasons, but the similar susceptibility of children or older patients who have not eaten for several days is not as familiar. It is not uncommon to find that a patient's recommended dosage of 'paracetamol 4 h prn' has resulted in a total ingestion of more than 4 g/day for several days or even weeks.

With her early dementia, MG could easily have been self-administering paracetamol (and/or paracetamol-containing analgesics) in large dosages for her joint pains, perhaps aided and abetted by caring relatives and nursing staff. Avoiding this potentially lethal 'iatrogenic' complication in contemporary medical practice should have greater priority.

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Table 1. Potentially hepatotoxic drugs

Drug/drug class	Spectrum of liver injury	Important hepatotoxic representatives of the group	Practice points
Anaesthetic agents	Acute hepatitis; acute liver failure	Halothane Newer agents (desflurane, sevoflurane) very rarely	Important cause of postoperative jaundice; more common in patients over 40 years of age, women, obese individuals, persons with a familial disposition and with repeated use
Antithyroid drugs	Acute or cholestatic hepatitis; acute liver failure	Propylthiouracil Carbimazole	Propylthiouracil more commonly used
Anti-tuberculous drugs	Acute hepatitis; liver failure	Isoniazid, rifampicin (with isoniazid), pyrazinamide (with isoniazid, rifampicin)	Risk increases with age (up to 1%), alcohol intake. Important to educate patients about symptoms of acute hepatitis. LFT monitoring recommended but should not replace early assessment of non-specific symptoms
Antibiotics	Acute or chronic hepatitis; cholestatic liver injury	Amoxycillin–clavulanate	Most common cause of idiosyncratic DILI; onset can be delayed for several weeks after completing antibiotic course. Genetic predisposition
		Flucloxacillin (cholestatic liver injury), nitrofurantoin, minocycline	Prolonged courses, IV use. Long-term nitrofurantoin and minocycline use can be associated with chronic hepatitis with autoantibodies
		Erythromycins, cephalosporins	Rare cases of cholestasis
Anti-convulsants	Acute hepatitis; granulomatous hepatitis; acute liver failure	Phenytoin	Personal or family history of anticonvulsant hypersensitivity (should avoid these agents)
		Carbamazepine	Granulomatous or cholestatic hepatitis
		Valproate (acute liver failure)	Valproate liver toxicity more common with mitochondrial enzyme deficiencies (and patients carrying certain mitochondrial gene polymorphisms), young children and with polypharmacy
Cardio-vascular drugs	Acute hepatitis; cholestatic hepatitis; rarely cirrhosis, acute liver failure	With exception of methyldopa and amiodarone, very rare reactions	–
		Methyldopa	Acute and chronic hepatitis, cirrhosis
		Labetalol	Acute hepatitis, acute liver failure
		Amiodarone	Abnormal liver tests, acute liver failure, steatohepatitis, cirrhosis. Note: opacification on CT due to iodine and not toxicity
		ACE inhibitors	Cholestatic hepatitis
Herbal medicines and other over-the-counter agents	Abnormal liver tests; acute and chronic hepatitis; acute liver failure; hepatic venous outflow obstruction	Germander; pyrrolizidine alkaloids; slimming aids containing usnic acid; black cohosh	Careful enquiry into herbal medicine use is critical. Not always in 'medicine' formulation, therefore ask about herbal tea mixtures, health supplements, over-the-counter medications
Highly active antiretroviral treatment (HAART)	Mitochondrial hepatotoxicity: steatosis, lactic acidosis, acute liver failure with first-generation NRTIs; less common with newer NRTIs (tenofovir)	Zidovudine, didanosine, stavudine	Baseline and serial liver test monitoring needed. Educate and encourage patients to report symptoms that could reflect liver injury/lactic acidosis
	Acute hepatitis with non-NRTIs	Nevirapine (acute hepatitis) High-dose ritonavir (acute hepatitis)	Drug interactions with protease inhibitors to be considered when multiple drugs are prescribed

Table 1. Potentially hepatotoxic drugs continued

Drug/drug class	Spectrum of liver injury	Important hepatotoxic representatives of the group	Practice points
Hormonal agents and hormonal antagonists	Cholestasis; hepatic adenoma; hepatocellular carcinoma	Oestrogens, anabolic steroids, antiandrogens: danazol, cyproterone acetate (cholestasis, hepatic adenoma, rarely hepatocellular carcinoma)	Avoid uninterrupted high-dose use of sex steroids. Physical examination (hepatomegaly) and consider serial hepatic imaging in long-term danazol and cyproterone acetate users
	Acute hepatitis; acute liver failure	Tamoxifen (steatohepatitis, rarely cirrhosis)	More common with underlying obesity and metabolic syndrome
Immuno-suppressive agents*	Hyperbilirubinaemia	Cyclosporin – not true 'toxicity' or cholestasis (effects on bile canalicular transporters)	May cause raised bilirubin, which does not reflect liver injury (it is a transport defect of no clinical significance)
	Cholestatic hepatitis; hepatic veno-occlusive disease; other vascular disorders of liver	Azathioprine	Particularly after renal transplantation, occasionally after several years
	Fibrosis; steatohepatitis; cirrhosis	Methotrexate	Risk factors: older age, alcohol use (more than 15 g/day), renal failure, obesity, fatty liver. Management: pre-treatment liver biopsy in selected cases; regular LFT monitoring; on treatment liver biopsy based on cumulative dose thresholds; liver tests and checking risk factors
Lipid-lowering drugs	Acute hepatitis; acute liver failure	Statins	Statin-related hepatotoxicity is very rare. Periodic monitoring of liver tests is unhelpful
		Nicotinic acid (acute liver failure)	Nicotinic acid hepatotoxicity is severe and partially dose-dependent
NSAIDs	Acute or chronic hepatitis; acute liver failure; cholestasis	Many potential culprits, including COX-2 inhibitors (lumiracoxib withdrawn because of hepatotoxicity)	Avoid NSAIDs in patients with cirrhosis for risk of causing gastrointestinal bleeding, acute renal failure
		Diclofenac (acute/chronic hepatitis); sulindac (cholestatic liver injury); ibuprofen (rare cholestasis)	Diclofenac hepatitis can mimic autoimmune hepatitis. Increases in serum transaminases reported with ibuprofen in persons with chronic hepatitis C
Paracetamol	Acute liver failure	Dose-dependent but check individual risk factors	Important to consider in cases presenting with an overdose 'staggered' over a few days. Identify individuals at risk of liver injury (prolonged fasting, alcoholics, late presentation or concealed use, concomitant medication use). Have a low threshold for testing paracetamol levels in emergency department
Sedatives, anti-depressants	Acute hepatitis; cholestatic hepatitis; cholestasis	Chlorpromazine (still a cause of cholestatic hepatitis) Amitriptyline, imipramine (cholestasis) Trazodone (acute and chronic hepatitis)	Several selective serotonin reuptake inhibitors have been associated with acute hepatitis, but reactions are very rare compared with older agents

*Before prescribing immunosuppressive or anticancer drugs, doctors must know each patient's hepatitis B status. Severe exacerbations, occasionally fatal, can occur with immune modulation for anyone (including 'healthy carriers') with chronic hepatitis B virus infection.

ACE = angiotensin-converting enzyme; COX-2 = cyclooxygenase 2; CT = computed tomography; DILI = drug-induced liver injury; IV = intravenous; LFT = liver function test; NRTI = nucleoside reverse transcriptase inhibitor; NSAIDs = non-steroidal anti-inflammatory drugs.

Investigations and Management

MG needs to have heart failure excluded clinically and with simple tests (such as a chest X-ray). In addition to thoroughly investigating possible exposure to other drugs, serum paracetamol estimation is still worth performing even though the onset of jaundice indicates that severe liver injury began 2 to 5 days earlier. If paracetamol is still detectable, this is suspicious for paracetamol as the cause of DILI.

Admission of MG to hospital is advisable unless it is against her and her family's expressed wishes (under a living will, for example). Although in this case it is past the optimal first 16 hours since paracetamol ingestion, most medical units would still administer *N*-acetylcysteine (NAC) as there is some evidence that NAC may ameliorate acute liver failure and it does not increase risks of hepatic coma and other complications. (NAC augments glutathione reserves and hence the inactivation of the toxic metabolites of paracetamol that accumulate when the drug is taken in large quantities.)

Case 3

BO has the odds stacked against him for further cardiac events as he has diabetes, multivessel coronary heart disease and atherogenic dyslipidaemia (low HDL cholesterol and very high LDL cholesterol levels). He should be prescribed a statin, and it is totally inappropriate not to do so. The evidence that statins reduce risk of further cardiac events is overwhelming, and their protective efficacy is considerable. Some patients still get inappropriate advice that they cannot safely use statins because of their abnormal liver test results.

This patient almost certainly has non-alcoholic fatty liver disease (NAFLD); the diagnosis could be partly confirmed by a hepatic ultrasound. At age 64 years, with type 2 diabetes and metabolic syndrome (he has central obesity, diabetes and atherogenic dyslipidaemia) and with markedly abnormal liver tests (particularly his ALT level of 150 U/L), there is a high probability that BO has cirrhosis complicating longstanding NAFLD (or, more specifically, its progressive form termed non-alcoholic steatohepatitis [NASH]).

Statins, however, despite their reputation and the information on the package insert, rarely cause any liver injury; about 3% of patients have raised ALT in clinical trials, with most changes resolving during continued drug administration. Monitoring ALT levels in patients taking statins is inconvenient, costly and ineffective, and in reality, statins are among the rarest causes (less than one case per 100,000 persons exposed) of clinically significant DILI.

Finally, and most cogently for this patient, pre-existing NAFLD, or abnormal liver tests from any cause of liver disease, does not predispose to statin-induced liver injury. The evidence on which the American Association for the Study of Liver Diseases (and all hepatologists) have reached this conclusion is based on millions of person-year exposures and prospective study by the National Institutes of Health DILI Collaborative Research Network.[2–5]

Case 4

JL would like to get back to work, so the odds of long-term liver complications from his restarting methotrexate need to be weighed against his clinical issues and social need for disease control.

Risk Factor Update

Before once-a-week low-dose (up to 25 mg) regimens of methotrexate were used, cases of methotrexate fibrosis culminating in cirrhosis, even hepatic decompensation or liver cancer, were not rare. Now that methotrexate is a first-line disease-modifying drug in rheumatoid arthritis and has other important indications including psoriasis, it is prescribed in dosage schedules that are rarely associated with significant liver fibrosis.

Some rheumatologists believe that methotrexate liver disease is a condition of the past, but there are important caveats, including the possibility that liver involvement is more common with psoriasis than with rheumatoid arthritis. Hepatology specialists still see rare cases of cirrhosis – but only when guidelines are disregarded.

Recommendations

The previous recommendation was that a liver biopsy is indicated after a patient has taken a total of 2 g methotrexate. However, this is probably not necessary unless the patient has had repeatedly abnormal liver test results (the American Rheumatological Association recommends LFTs every 2 to 3 months) and/or there are important risk factors for methotrexate-induced liver fibrosis.[2,6] These risk factors include 'significant alcohol intake' (15 g/day or more), diabetes, renal failure and obesity.

There is a strong suspicion that methotrexate exacerbates NAFLD/NASH, and patients with risk factors for this metabolic liver disease should be monitored closely (regular LFTs and consideration of liver biopsy) when taking methotrexate.

It is advisable that JL considers having a liver biopsy. A finding of his liver being normal after his taking 5 g methotrexate would give reassurance about the safety of restarting methotrexate, assuming there is no evidence of or risk factors for fatty liver disease.

Key points

- Drug-induced liver injury (DILI) is a significant cause of morbidity and can lead to liver failure.
- Few of the more than 300 agents implicated as possible causes of DILI are associated with a frequency of drug reactions greater than 0.1%.
- The agents most often responsible in DILI are those most commonly prescribed (ie, antimicrobials, NSAIDs and anticancer drugs). Generally, the agent started most recently is the most likely culprit.
- Diagnosis is vital as continued drug ingestion after onset of liver injury is a critical factor for poor prognosis.
- Patients are often unaware of the toxicity of large quantities of paracetamol.
- Statins rarely cause liver injury.
- The long-term risks of liver complications from methotrexate treatment should be weighed against the benefits of therapy.

JL should be counselled about safe levels of alcohol intake (less than 15 g/day) and have LFTs performed four times a year.[6] The LFT changes are usually non-specific minor elevations of ALT and/or GGT, but any fall in serum albumin level or platelet count could indicate developing cirrhosis. The indication for and timing of any subsequent liver biopsy will depend on the initial findings, and whether there are risk factors or liver test abnormalities. Thus, it should be an individualized approach and involve discussion between the specialists involved and the patient's GP.

If JL declines the offer of a liver biopsy, most hepatologists would not recommend withholding treatment with methotrexate, but clearly monitoring during the treatment and the prevention of risk factors would take on even greater importance. Non-invasive tests, including physical modalities of 'liver stiffness' (such as a transient elastography) and biochemical markers (such as serum hyaluronan) may soon be more widely applied in this context. Transient elastography is already available in many specialized liver units and could be valuable for assessment of severe fibrosis, but there is not yet a strong evidence base for the use of biochemical markers of hepatic fibrosis in patients taking methotrexate.

Conclusion

The key points about DILI that need to be borne in mind by GPs and all prescribing doctors are highlighted at the beginning of this article. While a vast number of agents have been associated with some form of liver injury, commonly used agents like antimicrobials and NSAIDs are most often involved. Always consider the temporal profile between drug ingestion and liver injury; the agent started most recently is typically the culprit when patients develop hepatitis or jaundice. Although exclusion of common disorders (viral hepatitis, gallstone, fatty liver disease) is an essential step towards diagnosis of DILI, it is helpful for doctors to always ask themselves whether a drug (prescribed or over-the-counter) or herbal remedy could be incriminated as the cause of individual cases of liver disease.

References

1. Chitturi S, Farrell GC. Hepatotoxic slimming aids and other herbal hepatotoxins. J Gastroenterol Hepatol 2008;23:366–373.
2. Chitturi S, Farrell GC. Drug induced liver disease. In: Schiff ER, Sorrell MF, Maddrey WC, eds. Schiff's diseases of the liver. 10th ed. New York: Lippincott Williams and Wilkins; 2007:923–1004.
3. Bader T. The myth of statin-induced hepatotoxicity. Am J Gastroenterol 2010;105:978–980.
4. Rzouq FS, Volk ML, Hatoum HH, Talluri SK, Mummadi RR, Sood GK. Hepatotoxicity fears contribute to underutilization of statin medications by primary care physicians. Am J Med Sci 2010;340:89–93.
5. Visser K, Katchamart W, Loza E, et al. Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. Ann Rheum Dis 2009;68:1086–1093.
6. Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents. J Am Acad Dermatol 2009;61:451–485.

Declaration of Interest

None.

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Ophthalmology

Reviews

- Conjunctivitis: Don't Miss the Serious Causes
- The Watery Eye: It's Worse Than You Think
- Angle Closure Glaucoma: An Overview

Common eye problems like conjunctivitis, the watery eye and angle closure glaucoma may be encountered in general practice. GPs need to recognize the symptoms for a better and early diagnosis with prompt referral.

How much do you know about ophthalmology?

	True	False
1. Cicatricial and traumatic types of conjunctivitis are less likely to have serious consequences.	☐	☐
2. Topical chloramphenicol and topical fluoroquinolone are best reserved for cases of bacterial conjunctivitis where cultures have proven sensitivity.	☐	☐
3. The problem of a watery eye is not rated highly by patients in terms of adverse impact on their quality of life.	☐	☐
4. The aim of clinical examination of the patient with a watery eye is to differentiate between overproduction of tears and defective drainage of tears.	☐	☐
5. Angle closure glaucoma accounts for almost half of the glaucoma cases and is emerging as a leading cause of blindness in Asian countries.	☐	☐

See page 188 for answers

Conjunctivitis: Don't Miss the Serious Causes

Freny Kalapesi, BSc(Med), MBBS, PhD, FRANZCO

Although most forms of infective and allergic conjunctivitis are not serious, some forms can, if not diagnosed early, lead to loss of sight or systemic morbidity. An understanding of the various causes of conjunctivitis and also the differential diagnosis of 'the red eye' helps to avoid missing these serious diagnoses and allows the opportunity to treat them in a timely manner when diagnosed.

Conjunctivitis can be infective, allergic, cicatricial and traumatic in origin.

Confronted with a patient with a red eye, more often than not the diagnosis is conjunctivitis. However, an automatic diagnosis of 'conjunctivitis' is often made without enquiry or consideration of possible alternatives. Treatment too often appears to be a 'trial of chloramphenicol' with or without topical corticosteroids, with referral if the red eye does not resolve. Although for most 'conjunctivitides' a short course of this empirical treatment may not harm the eye or alter the visual or systemic prognosis, for some entities a prolonged delay in appropriate investigation and treatment can be devastating.

A better understanding of the various types of conjunctivitis and also the differential diagnosis of 'the red eye' is imperative for better diagnosis and appropriate therapy and to avoid missing a potentially blinding or life-threatening illness.

Types and Causes of Conjunctivitis

The various types of conjunctivitis take their names from their causative processes. Conjunctivitis can be infective, allergic, cicatricial (scarring subtype), and traumatic in origin (see the box on page 170).

Diagnosing Conjunctivitis

With an adequate history and ocular examination, it is usually possible to form a working diagnosis for the subtype of conjunctivitis or to diagnose an alternative disease entity causing the red eye (differential diagnoses are

Types of conjunctivitis

Infective*

Bacterial
- Acute typical (including *Staphylococcus aureus*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*)
- Gonococcal
- Meningococcal
- Adult chlamydial (*Chlamydia trachomatis* serotypes D to K)
- Trachoma (*C trachomatis* serotypes A, B, Ba and C)

Viral
- Adenoviral
- Herpetic (herpes simplex [herpes simplex virus 1 and 2], herpes zoster [varicella zoster virus])
- Molluscum (molluscum contagiosum [molluscum contagiosum virus])

Allergic

Acute allergic
- Seasonal
- Perennial

Atopic

Vernal

Cicatricial

Autoimmune
- Ocular cicatricial pemphigoid
- Stevens–Johnson syndrome
- Atopic keratoconjunctivitis
- Linear IgA disease

Infective causes
- Trachoma
- Herpes zoster, herpes simplex
- Severe adenoviral

Trauma
- Chemical
- Irradiation
- Post-surgery

Skin diseases
- Scleroderma
- Rosacea

Secondary to drugs
- Topical eye drops: pilocarpine, timolol

Neoplastic
- Sebaceous cell carcinoma
- Ocular surface squamous cell neoplasia

Traumatic – iatrogenic

Chemical

Radiation

Surgery

Foreign body

*Neonatal ophthalmia is a subset of infective causes and can be caused by a variety of organisms.

Differential diagnoses of the red eye

Ocular surface disorders
- Corneal or conjunctival foreign body
- Dry eye
- Subconjunctival haemorrhage
- Conjunctivitis
- Blebitis – infection of a surgically induced drainage bleb (for the treatment of glaucoma)
- Keratitis – infectious, peripheral ulcerative or marginal keratitis
- Episcleritis or anterior scleritis

Ocular disease processes
- Acute angle closure glaucoma
- Inflammatory causes
- Anterior uveitis
- Posterior scleritis
- Sympathetic ophthalmia
- Infection – endophthalmitis or panophthalmitis

Orbital disease processes
- Carotid cavernous fistula
- Orbital cellulitis

Masqueraders
- Malignancy – sebaceous cell carcinoma, ocular surface squamous neoplasia, primary acquired melanosis rarely, lymphoma, Kawasaki's disease or Kaposi's sarcoma
- Amyloidosis
- Pyogenic granuloma

listed in the box on this page). The diagnosis can often be elucidated with a few macroscopic features (see the flowchart on page 171).

The features on history and examination that can help elicit the cause of the red eye are discussed below and summarized in the box on page 172.

History

The relevant history in a patient with a red eye includes the presentation, course and duration of the ocular symptoms, and knowledge of the presence of systemic features. There should also be enquiry into a recent upper respiratory tract infection or contact with a person with red eyes.

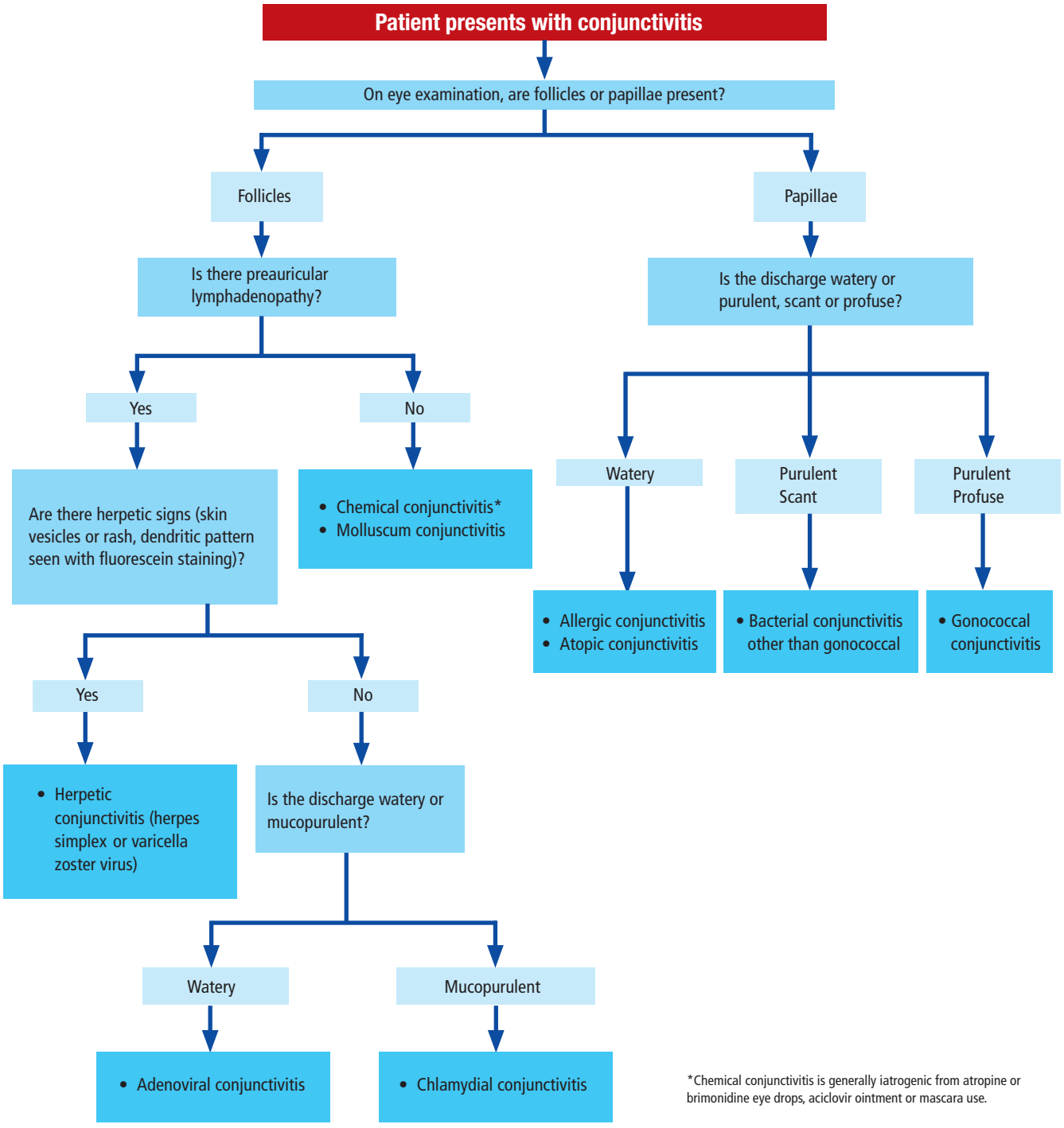
Examination

The presence of pain, localization of hyperaemia, nature of discharge present, presence of preauricular lymphadenopathy, presence of skin vesicles or typical dendritic fluorescein staining, presence of corneal infiltrates, and appearance of the palpebral conjunctiva (the internal aspect of the lid) can help elucidate the type of conjunctivitis.

The eye examination is augmented with the use of a slit lamp, which allows the findings of corneal infiltrates, fluorescein staining, localization of hyperaemia, and the differentiation of follicles from papillae (Figures 1 and 2).

For the general practitioner, this detailed examination is not always

Classification of conjunctivitis by ocular findings



*Chemical conjunctivitis is generally iatrogenic from atropine or brimonidine eye drops, aciclovir ointment or mascara use.

Clinical history and examination of a patient with red eye

History

- Recent upper respiratory tract infection; contact with people with red eyes
- Chronicity – history longer than 2 to 3 weeks (less likely to be viral conjunctivitis)
- Sinister features – tinnitus, pain, nausea or vomiting
- Known connective tissue diseases
- Evidence of sepsis (if unilateral and accompanying lid oedema/erythema, ± diplopia)
- Reduction of vision, halos, glare or photophobia

Examination

- Injection
  - Layer
    - conjunctival
    - episcleral
    - scleral

  Clue: blanching with 2.5% phenylephrine eye drops suggests conjunctivitis or episcleritis rather than scleritis; being able to move the conjunctiva over the injection after instillation of topical anaesthetic suggests scleritis
  - Location
    - unilateral versus bilateral
    - diffuse versus sectoral
    - perilimbal versus panconjunctival up to fornices
- Nature of discharge
  - Watery
  - Mucopurulent
  - Mucoid
  - Purulent
- Follicles versus papillae on the conjunctival aspect of the lids
- Presence of fluorescein staining
- Presence of corneal infiltrates (white spots)
- Presence of preauricular lymphadenopathy
- Pupil shape
  - Miosed or ovalized (acute glaucoma)
  - Asymmetrical (acute uveitis; Figure 3c)
- Extraocular motility if orbital cellulitis suspected

possible because of the lesser magnification without a slit lamp. However, eversion of the lids, fluorescein staining and examination with some form of magnification together with a cobalt blue light will aid initial examination.

Ocular Examination Findings

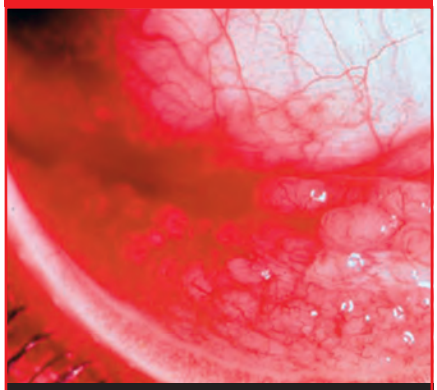
Conjunctival Injection

In viral conjunctivitis, conjunctival injection is often more marked towards the fornix (Figure 3a). In viral or allergic conjunctivitis, the injection is often bilateral, although it may be asymmetrical or unilateral. In contrast, in acute angle closure glaucoma and acute uveitis, the conjunctival injection is often more marked adjacent to the limbus (junction of the corneal periphery with the conjunctiva) and is described as ciliary injection (Figures 3b and c).

Episcleritis can be focal or diffuse, and injected vessels blanch in the presence of topical phenylephrine (2.5% is commonly used). In scleritis, the dilated vessels lie deeper and do not move on application of a cotton bud after topical anaesthetic or blanch with the application of topical phenylephrine. Scleritis can be focal or diffuse in its localization but is almost always accompanied by severe, deep, boring pain.

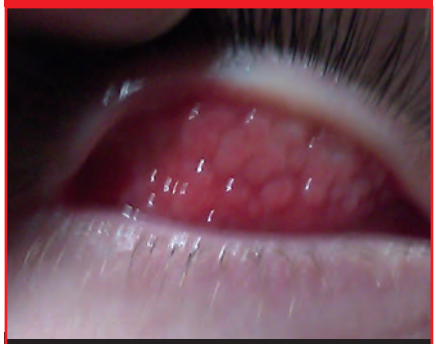
In allergic ocular processes, the signs tend to be more inferior in location in atopic keratoconjunctivitis and superior in vernal keratoconjunctivitis.

Figure 1.



Follicles – which can be seen in viral conjunctivitis. Note the rice grain appearance.

Figure 2.



Macropapillae – which can be seen in moderate to severe allergic eye disease and with contact lens wear. Note the cobblestone appearance.

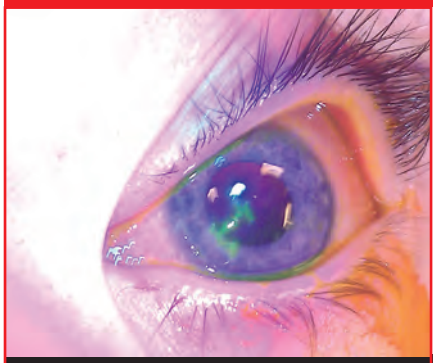
Follicles or Papillae

Follicles (collections of inflammatory cells with germinal centres) typically look like small grains of rice and have vessels encircling the follicle (Figure 1). They are most prominent in the fornices and are typically present in viral conjunctivitis (that due to the common adenoviral sero types and also epidemic adenoviral kera-

Figure 3. Conjunctival injection.

a. Viral conjunctivitis. Conjunctival injection, although often asymmetrical, has a tendency towards bilaterality and is more intense towards the fornix rather than the limbus. **b** and **c.** Acute uveitis showing (b) the typically unilateral conjunctival injection, with (c) ciliary injection and less dense injection at the fornices. The ciliary injection is most notable inferior and temporally (as medially there is more diffuse injection). The pupil is not round owing to posterior synechiae (as the iris has become adherent to the anterior lens surface).

Figure 4.



Dendritic staining typical of herpes simplex keratitis.

toconjunctivitis, as well as herpetic keratoconjunctivitis and that due to molluscum contagiosum virus), trachoma, adult chlamydial conjunctivitis and in the presence of mascara.

In contrast, papillae typically have a cobblestone appearance and range in size from micropapillae to macropapillae (less than 1 mm) to giant papillae (more than 1 mm and visible with the naked eye), dependent on the duration and nature of the inflammation (Figure 2). Papillae have a central fibrovascular core, and hence vessels appear central on slit lamp examination. Papillae are typical of allergic eye diseases, bacterial conjunctivitis, floppy eyelid syndrome associated with sleep apnoea in obese individuals, and contact lens wear.

Discharge

The nature and severity of the discharge is also helpful in differentiating the cause of conjunctivitis. Copious purulent discharge, especially in a newborn infant, can herald sight-threatening gonococcal keratoconjunctivitis with the risk of ocular perforation. Purulent discharge is more typical of bacterial infections, whereas watery discharge (as in Figure 3a) is more typical of viral infections and is usually accompanied by preauricular lymphadenopathy. Mucopurulent discharge can be typical of trachoma or other chlamydial infections.

Discharge or the presence of a watery eye in a newborn needs careful evaluation. It can be a common finding of nasolacrimal duct obstruction. It may be the only sign of congenital glaucoma or serious neonatal ophthalmia (conjunctivitis in the neonate). Neonatal conjunctivitis can be due to common bacteria (such as *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae* or *Escherichia coli*), but it can also be due to sexually transmitted infections such as chlamydia and gonorrhoea.

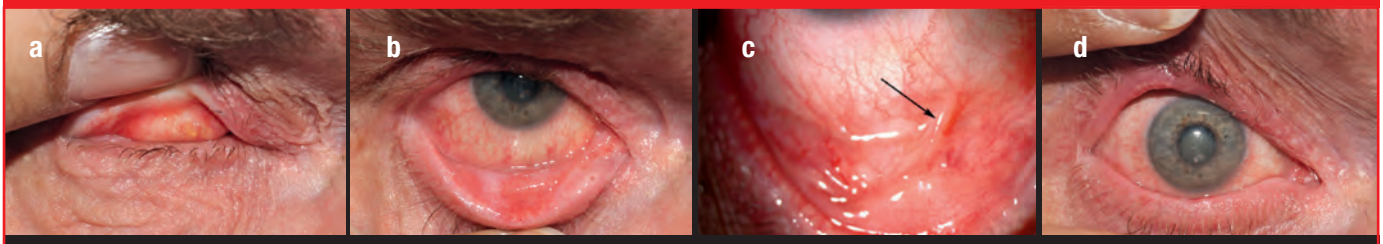
Neonatal conjunctivitis warrants treatment not observation, and management should involve specialist paediatric care. Systemic treatment may be required in addition to local treatment, and investigation for the source of the infection warrants serious attention because of systemic risks.

Fluorescein Staining

The use of fluorescein staining accompanied by slit lamp examination under cobalt blue light may reveal a dendritic pattern to the staining (Figure 4). This is typical of herpetic keratitis (with terminal bulbs in herpes simplex keratitis or without terminal bulbs in herpes zoster keratitis) but may also be seen in a healing corneal epithelial defect, a recurrent corneal erosion or a neurotrophic corneal ulcer.

Fluorescein staining tends to be vertical and linear in the presence of a subtarsal foreign body (lying

Figure 5. Signs of cicatrising conjunctivitis.



a and **b**. Subtarsal scarring under the (a) upper and (b) lower lids. **c.** Symblepharon (arrow) in the inferior fornix, which is shortened. **d.** Late cicatricial disease with corneal vascularization and opacity and trichiasis.

on the upper lid tarsal conjunctiva) and punctate and inferior in cases of corneal exposure (due to poor eyelid closure or a poor blink).

Corneal Infiltrates

Corneal infiltrates (small white opacities in the superficial cornea) may be present in adenoviral conjunctivitis (and may degrade vision). They can also occur superiorly in adult chlamydial conjunctivitis. They are a result of white cell recruitment with or without an infective component.

Subtarsal Scarring and Other Features

Examination of the underside of the eyelids and also of the plica and caruncle can help in determining a diagnosis of cicatricial conjunctivitis.

Subtarsal scarring (scarring of the conjunctival under the eyelid, typically the upper eyelid) can be a finding of trachoma, ocular cicatricial pemphigoid, atopic or vernal eye disease and even severe adenoviral keratoconjunctivitis (Figures 5a and b). Accompanying features such as symblepharon (fibrotic bands present between the internal aspect of the lid and the exposed interpalpebral portion of the conjunctiva) and loss of the contour of the plica and caruncle (the specialized fold or bump on the medial aspect of the conjunctiva) due to keratinization of the caruncle can point to a particular cicatrising ocular process (Figure 5c). Corneal vascularization and opacity and trichiasis are features of late cicatricial disease (Figure 5d).

'Serious' Conjunctivitis

Although most forms of infective and allergic conjunctivitis are considered 'non-serious', they can occasionally present with 'serious' consequences to vision and or general health. Cicatricial and traumatic types of conjunctivitis are more likely to have serious consequences.

When forming a diagnosis of conjunctivitis, it is extremely important to be aware of those conjunctivitides that can, if not diagnosed and treated, lead to loss of sight or systemic morbidity, and possibly even mortality.

If a serious conjunctivitis is suspected, investigations can aid in diagnosis. This could include microbiology (conjunctival swabs), histopathology (scrapes or biopsies), and measuring intraocular pressure.

Ocular Cicatricial Pemphigoid

If cicatricial signs are elucidated, ophthalmic referral is paramount. The ophthalmologist will determine, usually in conjunction with other physicians (particularly an immunologist), the cause of cicatricial conjunctivitis (see the box on page 170).

Without treatment, ocular cicatricial pemphigoid can progress inexorably with scarring of the lids, conjunctiva and cornea, causing irreversible loss of sight. This is worsened by the obstruction of lacrimal ductules and tarsal (Meibomian) gland openings, leading to a severe dry eye. Diagnosis requires a biopsy of an involved mucosal area, and treatment involves multidisciplinary care with systemic immunosuppression being the mainstay of treatment together with topical treatments.

Serious Presentations of Infective Conjunctivitides

Severe Adenoviral Conjunctivitis

Adenoviral conjunctivitis is the most common cause of bilateral, often asymmetrical, red eyes. It is usually a benign, self-limiting disease process requiring only eye and hand hygiene as well as isolation to avoid spread. Local lubrication and cool compresses can help symptomatically.

Aggressive adenoviral keratoconjunctivitis can occur and can manifest with subtarsal scarring and corneal subepithelial infiltrates, leading to reduction of vision (Figure 5a). The usual presentation is following exposure to a viral upper respiratory tract infection or contact with a person with red eyes. Investigation is usually

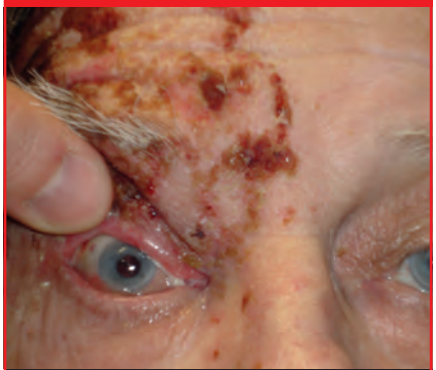
not required, but if the diagnosis is in doubt or the condition fails to resolve in the anticipated time frame then a conjunctival swab can be taken for confirmation of the diagnosis by adenoviral DNA testing using the polymerase chain reaction (PCR) technique.

Ophthalmic treatment may be warranted for severe disease. This may involve gentle peeling of subtarsal membranes, or the use of topical corticosteroids for subtarsal scarring, membranes or subepithelial corneal infiltrates that degrade vision. It is the opinion of this author that topical corticosteroids should only be prescribed by an ophthalmic professional capable of measuring intraocular pressure and treating any ensuing complications from topical corticosteroid usage. Some ophthalmologists advocate the use of topical dilute povidone iodine (2.5–5%) to speed eradication of viral titres; while this can help rapidity of improvement, it can induce ocular surface discomfort on application.

Herpetic Conjunctivitis and Other Herpetic Ocular Manifestations

Diagnosing herpetic conjunctivitis can be either straightforward when the presence of skin vesicles typical of herpes simplex or the rash of herpes zoster (shingles) is clear, or less obvious and require asking about the presence of dysaesthesia, previous or current symptoms of cold sores and looking for subtle features of these (Figure 6). Conjunctival swabs can be taken for herpes simplex virus 1 and 2 and varicella zoster virus testing by PCR.

Figure 6.



Zoster blepharoconjunctivitis and right divergent squint consistent with a zoster-induced right third nerve palsy.

Ocular suspicion of herpetic eye disease warrants ophthalmic referral to ascertain if intraocular manifestations are present. These can include corneal disease, uveitis, trabeculitis, devastating retinitis and cranial nerve palsies (Figure 6).

Treatment varies according to the diagnosis and usually involves topical antivirals with or without topical corticosteroids for herpes simplex and oral antivirals with or without topical corticosteroids for herpes zoster. Uveitis requires topical corticosteroid treatment, trabeculitis requires intraocular pressure-reducing medications in the first instance, and treatment of retinitis is beyond the scope of this brief review.

Gonococcal Conjunctivitis

The presence of a hyperacute (within 12 to 24 hours) severe purulent conjunctivitis should warrant suspicion of gonococcal conjunctivitis. This condition can be indistinguishable (apart from profuse purulent discharge) from severe adenoviral conjunctivitis, as both can cause severe eyelid oedema, erythema, subtarsal membranes and preauricular lymphadenopathy, although the presentation of gonococcal disease is more acute. At-risk patient groups include neonates and sexually active individuals.

Gonococcal conjunctivitis can be diagnosed by microscopy and culture of a conjunctival swab, requesting an urgent Gram stain (looking for the Gram-negative diplococci of *Neisseria gonorrhoeae*). This is best done in a tertiary referral centre so that active management can be instituted as soon as possible. Establishing *N gonorrhoeae* as the offending organism is extremely important because untreated corneal ulceration can occur with rapid progression to corneal perforation and loss of the eye. Treatment involves systemic treatment with ceftriaxone, ocular irrigation and investigation for other sexually transmitted diseases (especially chlamydia).

Adult Chlamydial Conjunctivitis

Adult chlamydial conjunctivitis (caused by *Chlamydia trachomatis* serotypes D to K) is an important diagnosis to make because systemic chlamydial infection can cause female infertility, be a trigger for Reiter's disease in men, and cause pneumonitis.

Ocular manifestations include a stringy mucopurulent discharge, follicles and possibly peripheral corneal subepithelial infiltrate. Investigation includes conjunctival swabs/scrapes for PCR or immunofluorescent probes and culture. A systemic antibiotic (usually a stat dose of azithromycin or a course of oral doxycycline) for the patient and their sexual contacts is usually curative. Definitive referral and co-management with sexually transmitted infection physicians is mandatory so that diseases such as syphilis and HIV can be excluded.

Trachoma

A diagnosis of trachoma (caused by *C trachomatis* serotypes A, B, Ba and C) is usually made in endemic regions where the water supply and washing facilities are poor and poverty and overcrowding are prevalent. It

remains the leading cause of preventable blindness worldwide and is still prevalent among rural Aboriginal Australians.

The ocular findings include follicles, thickening of the tarsal conjunctiva, subtarsal scarring, trichiasis (posterior misdirection of lashes) and corneal scarring/opacity. Prevention and health initiatives aimed at population screening, antibiotics for patients with active disease or living in endemic regions, improved water supplies and washing facilities and control of flies remain the mainstay of treatment. Lid complications and scarring may warrant eyelid surgery to treat trichiasis and reposition the lid lamellae.

Ophthalmia Neonatorum

Mucopurulent discharge from one or both eyes in the first 4 to 6 weeks of life accompanied by injection of the conjunctiva warrants consideration of serious causes of ophthalmic neonatorum. Important differential diagnoses include nasolacrimal duct obstruction, dacrocystitis (caused by infection and blockage at the level of the lacrimal sac), and congenital glaucoma.

Any non-resolving purulent discharge in a newborn warrants urgent referral to an ophthalmologist. Organisms involved are usually common bacteria (including staphylococci, streptococci and Gram-negative organisms). However, serious causes include *N gonorrhoeae* (where corneal ulceration/perforation as well as arthritis can occur), *C trachomatis* (where pneumonitis, otitis media and infertility are a concern) and herpes simplex virus (where encephalitis and meningitis can rapidly ensue in the young if systemic antivirals are not commenced).

These patients are usually admitted and investigated with swabs and cultures and treated empirically, with treatment altered based on the results of Gram and Giemsa stains initially and then later based on culture results. Systemic antibiotics are required for both gonococcal and chlamydial disease and systemic antivirals for herpetic disease. Additionally if either *N gonorrhoeae* or *C trachomatis* is the causative organism, investigation and treatment of the mother and her sexual contacts are required.

Other Bacterial Conjunctivitis

Other types of bacterial conjunctivitis, such as that caused by *H influenzae* or *Neisseria meningitidis* (meningococcal conjunctivitis), carry systemic risks of otitis media, pneumonia, and meningitis. A 'wait and watch' approach is reasonable in adults as most cases self-resolve, although treatment hastens resolution. Treatment should be initiated in neonates.

Investigations, including microbiology, histopathology and measuring intraocular pressure, can aid in the diagnosis of serious conjunctivitis.

Allergic Conjunctivitis

Most cases of allergic conjunctivitis are relatively benign, with local symptoms such as itch, grittiness and ropy discharge. However, severe cases of atopic and vernal keratoconjunctivitis can occur, causing significant visual and ocular morbidity. Vernal conjunctivitis can be the cause of severe corneal disease (including shield ulcers and plaques, corneal vascularization, corneal opacity, and secondary bacterial and viral keratitis). Likewise, atopic conjunctivitis can cause severe lid and corneal disease.

Management of severe allergic processes requires a team approach with immunology, dermatology and ophthalmology specialist involvement. Local (topical)

lubricants, corticosteroids, mast cell stabilizers and cyclosporin are used, as well as systemic medications. Immunosuppression may be needed in particularly severe disease processes. Shield ulcers and plaques may require debridement and even corneal surgery to allow for healing. Frequent counselling regarding avoidance of eye-rubbing is important as this action can aggravate visual disease with subsequent development of or progression to keratoconus and the associated risk of retinal detachment.

Non-'conjunctivitides'

When considering a diagnosis of conjunctivitis, it is essential that other causes of the red eye are excluded, including keratitis, orbital infection or congestion, blebitis, anterior uveitis, endophthalmitis, and angle closure glaucoma (see the box on page 170).

Specialized ophthalmic equipment is required to look for the presence of a corneal infiltrate, examine the conjunctiva in all quadrants, examine for corkscrew vessels, examine for cells in the anterior chamber (and possibly in vitreous also), and to check the intraocular pressure. Therefore, referral should not be delayed if serious diagnoses are being entertained.

Associated lid erythema and oedema or diplopia could be a sign of an orbital infection, especially if accompanied by fever or signs of sepsis. Assessing vision, pupillary reactions, colour and contrast saturation, and visual fields to confrontation are required to exclude an optic neuropathy associated with orbital disease processes.

Delayed diagnosis of orbital cellulitis or carotid cavernous fistula could have devastating consequences, including cavernous sinus thrombosis (both processes), meningitis (infective orbital cellulitis), cerebral haemorrhage (carotid cavernous fistula), and death. Peripheral ulcerative keratitis could lead to ocular perforation without systemic immunosuppression. Acute glaucoma could lead to loss of vision from acutely raised intraocular pressures, and acute uveitis could lead to abnormalities in the pupil shape (synechiae), cystoid macular oedema, cataract, and glaucoma. Missing a masquerader such as sebaceous cell carcinoma could lead to loss of life.

Conclusion

In a person with a red eye, it is pertinent to take a complete systemic history including onset and course of the disease process and to look for associated systemic or ocular findings. Previous ocular history is essential. An ophthalmic examination including assessment of vision, inspection of the discharge, inspection for the presence of lid vesicles or a rash, inspection for the presence of subtarsal follicles or papillae, localization of the hyperaemia and fluorescein staining, and inspecting for cicatrising features are required as a bare minimum. Enquiry regarding suspicious features, including diplopia, limited ocular motility, pain, and reduction in vision, is essential.

Although topical chloramphenicol and topical fluoroquinolone are commonly prescribed, they are best reserved for cases of bacterial conjunctivitis where cultures have proven sensitivity. Antibiotic resistance is on the rise, hence thoughtful prescription of antibiotics is necessary. Knowledge regarding the dangers of prescribing topical corticosteroids unmonitored, such as ocular hypertension and exacerbation of ocular infections, is required.

When a diagnosis is in doubt, conjunctival swabs can be of help if considering infection. Referral to an ophthalmologist should not be delayed as adequate treatment requires establishment of the disease process and specific treatment rather than empirical treatment.

Declaration of Interest

None.

Further Reading

Bhattimt, Peters KR. A red eye and then a really red eye. Surv Ophthalmol 2003;48:224–229.

College of Optometrists. Clinical management guidelines. Conjunctival scarring. Version 4. London: College of Optometrists; 2009.

Friedlaender MH. Conjunctivitis of allergic origin: clinical presentation and differential diagnosis. Surv Ophthalmol 1993;38(Suppl):105–114.

Jackson WB. Differentiating conjunctivitis of diverse origins. Surv Ophthalmol 1993;38(Suppl):91–104.

Kane KY, Meadows S, Ellis MR. Clinical inquiries. When should acute nonvenereal conjunctivitis be treated with topical antibiotics? J Fam Pract 2002;51:312.

Kanski JJ. Clinical ophthalmology. A systematic approach. 6th ed. London: Elsevier; 2007. Chapter 8. pp 215–248.

Rose PW, Ziebland S, Harnden A, Mayon-White R, Mant D. Why do general practitioners prescribe antibiotics for acute infective conjunctivitis in children? Qualitative interviews with GPs and a questionnaire survey of parents and teachers. Fam Pract 2006;23:226–232.

Shield JA, Demirci H, Marr BP, Eagle RC Jr, Shields CL. Sebaceous carcinoma of the ocular region: a review. Surv Ophthalmol 2005;50:103–122.

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The Watery Eye: It's Worse Than You Think

Geoff Wilcsek, MBBS(Syd), FRANZCO; Ian C Francis, OAM, MBBS(Syd), FRACS, FRANZCO, FASOPRS, PhD(NSW)

A watery eye, which is due to a mismatch between the volume of tears produced and the volume of tears removed via the lacrimal drainage system, can have a substantial adverse impact on an individual's quality of life.

A watery eye can have an adverse impact on an individual's wellbeing.

The impact of a watery eye on an individual's wellbeing is commonly underestimated. However, patients with this problem rate it highly in terms of adverse impact on their quality of life. A 'wet eye' and tear overflow may cause embarrassment, as well as blurring of vision that results in difficulty reading, an increased risk of falls, and loss of driving confidence. Repeated wiping of the lids may result in lid laxity, ectropion, and a dermatitic excoriation of the skin.

The cause of watery eyes can generally be determined by the family physician. With recent advances in diagnostic and surgical techniques, the definitive management of the watery eye is most commonly dealt with by ocular plastic surgeons, who comprise a subspecialty within ophthalmology.

The physiology of tearing is discussed in the box on page 179. The assessment and management of a patient with a watery eye is summarized in the flowchart on page 180.

Patient Assessment

History

When questioning the patient with a watery eye, it is necessary to determine whether the problem is due to excess tear production (which is unusual) or inadequate drainage of tears away from the eye (which is common).

It is important to ask the patient about ocular irritative symptoms that precede tearing. Ocular surface irritation causes a reflex (and indeed protective) overproduction of tears, which results in tearing even in the presence of a normal lacrimal drainage system. Conditions that irritate the ocular surface include:

- ectropion – the lower lid rolls out and exposes the inside surface of the lid to air. The exposed lid becomes dessicated, with resulting inflammation of the exposed conjunctiva of the lid. There is secondary malposition of the lacrimal punctum of the lower lid, which further increases the tearing.
- entropion – the lower lid intermittently rolls over on itself, causing the eyelashes to touch the cornea. The irritative symptoms are often relapsing, with intervening symptom-free periods.
- trichiasis – aberrantly-growing lashes are directed towards the cornea while the lid maintains its normal position. The ocular irritation is thus more constant than irritation owing to entropion.

Physiology of tearing

Tears are produced principally by the lacrimal gland, which is situated anteriorly in the superotemporal quadrant of the orbit. Tears wash over the eye and are important in maintaining a healthy ocular surface.

On blinking, tears are actively pumped through the upper and lower lacrimal puncta of the eyelids into the lacrimal sac (the lacrimal pump). The tears drain down the nasolacrimal duct, which opens within the inferior meatus under the inferior turbinate in the nose, and then flow posteriorly into the nasopharynx.

A tearing or watering eye is largely evidence of a mismatch between the volume of tears produced and the volume of tears removed via the lacrimal drainage system.

- blepharitis – chronic inflammation of the eyelid. Associated skin disorders of either rosacea or seborrhoeic dermatitis are often present.
- any ocular foreign body.

Tears contain numerous enzymes, including lysozyme, and overflow onto the skin can cause an excoriating dermatitic reaction. Patients often confuse ocular surface irritative symptoms with symptoms related to excoriation of the periorbital skin. For adequate management, it is important to take this into consideration when first questioning the patient.

A brief sinus history is useful because pathology of the maxillary and ethmoid sinuses can affect tear flow within the nasolacrimal duct.

Examination

The aim of the clinical examination is to differentiate between overproduction of tears and defective drainage of tears. The fluorescein tests described below are useful (with care taken to avoid spilling fluorescein onto the patient's clothes). Tearing due to poor drainage can be related to:

- upper system obstruction (from lacrimal punctum to common canaliculus)
- lacrimal pump dysfunction (eg, poor blinking, such as with involutional changes, facial palsy and Parkinson's disease)
- lower system obstruction (from lacrimal sac to nasolacrimal duct/nose).

Simple digital pressure over the lacrimal sac may enable the clinician to feel the normal concavity of the lacrimal sac region. Sometimes, a mucocele can be palpated; the application of pressure over the mucocele may occasionally allow large quantities of mucopus to reflux into the eye.

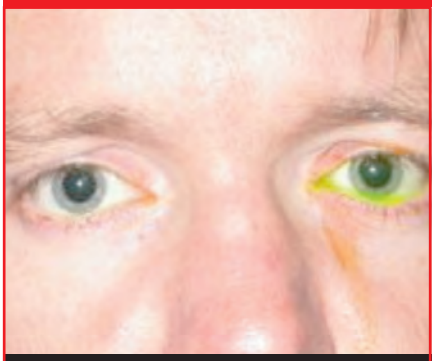
Fluorescein Dye Disappearance Test

To perform the fluorescein dye disappearance test, the tear film is stained with one drop of 2% fluorescein bilaterally. After 5 minutes, the patient is examined to see whether the tears are still fluorescein-stained. The absence of fluorescein (negative test) in the tearing patient suggests increased tear production but reasonable tear drainage. The presence of fluorescein and a high tear meniscus (positive test) indicates defective tear drainage (Figure 1).

Jones I and II Tests

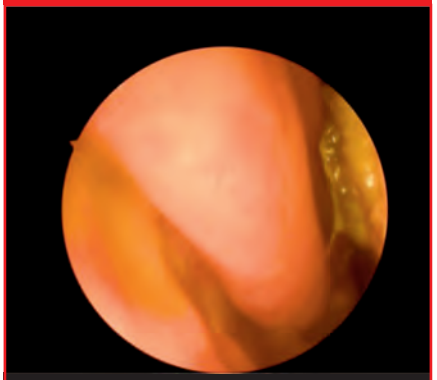
When inadequate tear drainage is detected, it is necessary to determine whether this is due to an upper system and/or pump problem or to a drainage problem. The Jones fluorescein tests are useful, allowing the clinician to determine whether tears reach the distal end of the nasolacrimal duct within the inferior meatus of the nose. Jones described the test using a cotton tip, which is placed under the inferior turbinate before 2% fluorescein (one to two drops) is instilled in the tears, and inspected after 5 minutes for fluorescein staining. Nasal endoscopy has

Figure 1.



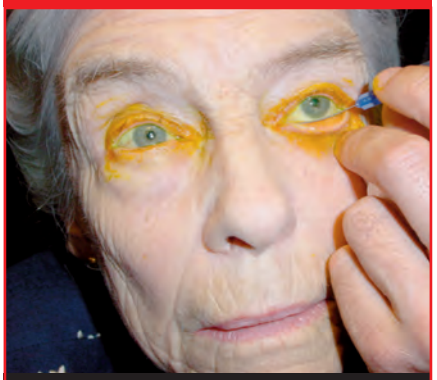
A positive fluorescein dye disappearance test with a raised marginal tear film (high tear meniscus).

Figure 2.



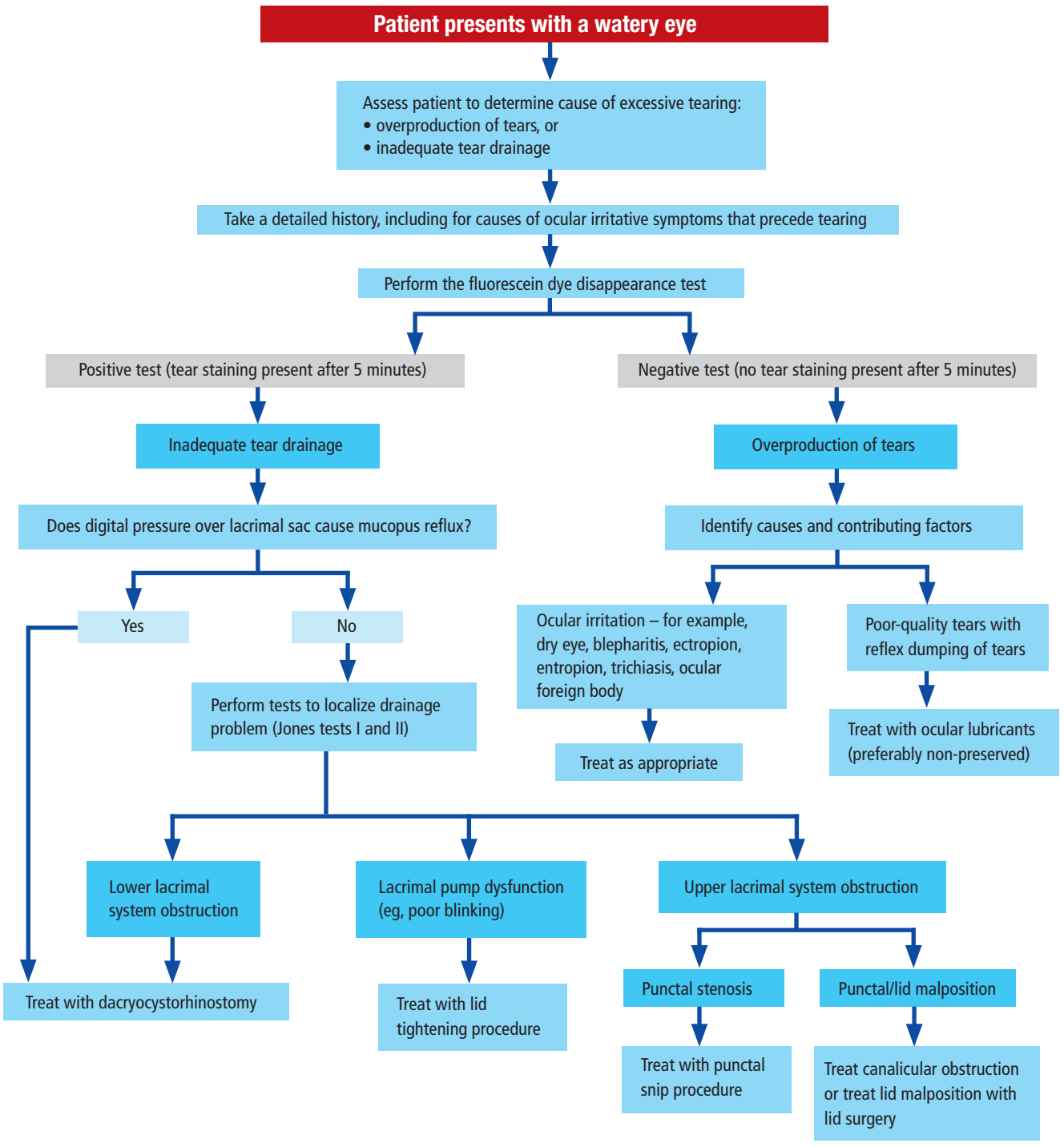
Nasal endoscopy demonstrating the presence of fluorescein (positive Jones I test).

Figure 3.



Simple lacrimal irrigation to flush tears through the lacrimal drainage system.

Assessment and management of the watery eye



Dacryocystorhinostomy

Dacryocystorhinostomy (DCR) is a procedure to treat a narrowed or blocked nasolacrimal duct in which a fistula is created between the lacrimal sac and the lateral wall of the nose (Figure 4).[1,2] This allows tears to pass directly from the lacrimal sac (Figure 5) into the nasal cavity, bypassing the blocked nasolacrimal duct. Figure 6 demonstrates intraoperative surgical opening of the lacrimal sac in the case of obstructed lacrimal drainage with immediate release of mucopurulent material into the nose prior to definitive creation of the mucosa-lined fistula.

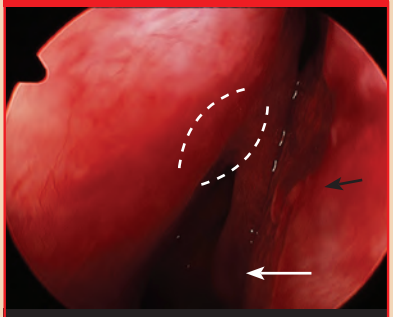
Towards the conclusion of the procedure, fine silicone stents are placed via the canaliculi into the nose (Figures 7 and 8). These are temporarily secured with a dissolvable cellulose pack railroaded around the silicone stents to keep the flaps of the opened lacrimal sac in place. The silicone stents are removed in the doctor's rooms 3 weeks postoperatively, and the patient is subsequently reviewed at 10 to 12 weeks to ensure that the ostium is patent (Figure 9).

Historically, DCR has mostly been performed via an external skin incision on the side of the nose. However, since the advent of powered instrumentation and the development of new endonasal techniques, the procedure is now often performed endoscopically via a transnasal approach under direct vision. The external and endoscopic procedures both take approximately 40 minutes to complete and are performed as day surgery with equal success rates (> 92%).[3,4] External DCR is usually performed under a local anaesthetic with sedation. Endoscopic DCR is typically performed under general anaesthesia because the noise and irrigation from the mechanized drill can be bothersome to the patient.

Endoscopic DCR has several advantages. A transnasal approach allows the surgeon to deal with conditions that may occlude the intranasal portion of the ostium formed during the DCR procedure – for example, an enlarged pneumatized middle turbinate (concha bullosa), significant septal deviation, or inflammatory polyps. In addition, a skin incision and scar on the face are avoided in endoscopic DCR.[5]

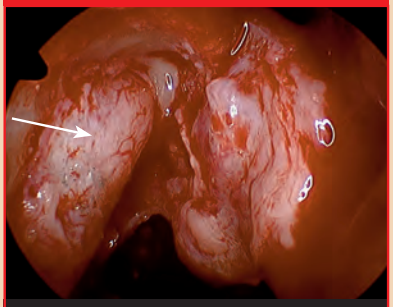
External DCR can potentially compromise the lacrimal pump mechanism because the inferomedial fibres of the orbicularis are disturbed in order to access the lateral wall of the nose via a skin incision.

Figure 4.



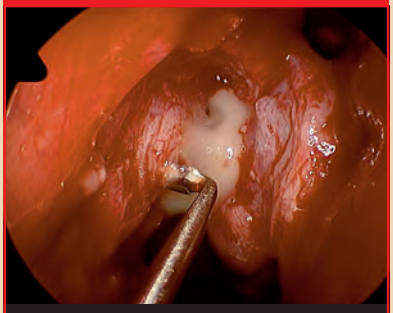
Typical view of the lateral wall of the nose showing the position of the lacrimal sac (oval), nasal septum (black arrow) and middle turbinate (white arrow).

Figure 5.



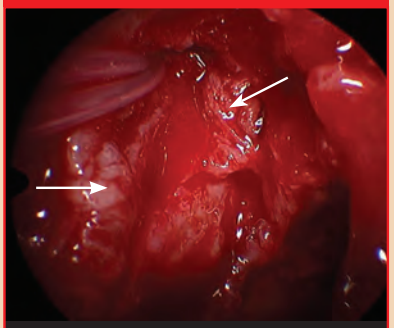
Exposed lacrimal sac (arrow) following bone removal.

Figure 6.



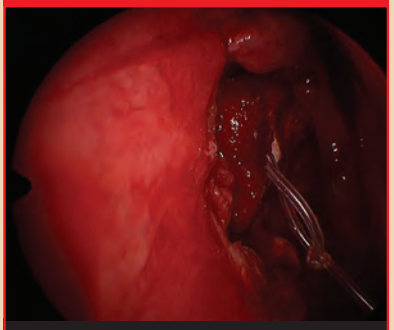
Incision into the lacrimal sac with release of pus.

Figure 7.



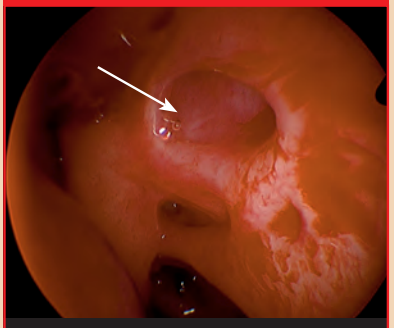
Newly fashioned lacrimal sac flaps (arrows).

Figure 8.



Stents placed to hold the flaps in place until they heal.

Figure 9.



A mature fistula (arrow) successfully bypassing the obstructed nasolacrimal duct.

rendered the test more accurate, more comfortable, and simpler to perform (modified Jones test). A combined lignocaine/phenylephrine spray is applied to both nostrils to anaesthetize and decongest the nose, before fluorescein is instilled into the tears. Using a 30-degree rigid endoscope, the distal end of the nasolacrimal duct is then inspected (Figure 2).

Detection of fluorescein in the nose indicates that the nasolacrimal duct is patent (positive Jones I test). If no fluorescein reaches the nose (negative Jones I test), then saline is used to irrigate the system and flush through any tears that have entered the lacrimal system but become held up at a stricture in the nasolacrimal duct (Jones II test). The irrigation is carried out using a 25-gauge lacrimal cannula attached to a 3-mL saline-filled syringe. The cannula is placed into the lower canaliculus and saline irrigated through the lacrimal system (Figure 3). The inferior meatus is again inspected endoscopically for fluorescein-stained tears.

If the nasolacrimal duct is completely obstructed, the Jones I test will be negative. On syringing, saline will hit the obstruction and reflux back out the punctum of the ipsilateral upper lid, and no fluorescein will be irrigated into the inferior meatus (negative Jones II test). If there is partial obstruction or narrowing of the nasolacrimal duct, syringing saline will flush fluorescein-stained tears into the inferior meatus (positive Jones II test).

If there is an upper system obstruction (punctum or canaliculus) or lacrimal pump dysfunction, then no fluorescein-stained tears will enter the lacrimal drainage system to be flushed through with saline (negative Jones I and II tests).

The Jones test results in the patient with a watery eye are summarized below:

- Negative Jones I and II tests together with normal flow through the canaliculus into the nose from the saline lacrimal sac washout indicates that the drainage hold-up is in the upper lacrimal system, before the lacrimal sac. Treatment is aimed at repairing the lacrimal pump or lid position.
- Negative Jones I and II tests together with no flow into the nose from the saline lacrimal sac washout indicates complete obstruction of the lower system (lacrimal sac or nasolacrimal duct). It is treated by dacryocystorhinostomy (DCR).
- A negative Jones I test and positive Jones II test indicates that there is a significant narrowing in the lower lacrimal system. It is treated by DCR.
- A positive Jones I test indicates that the nasolacrimal duct is patent.

Treatment

For Overproduction of Tears

It is important to treat the cause of the tear overproduction. Lid malposition such as entropion or ectropion is best treated surgically. Trichiasis is treated with various therapies, ranging from regular epilation to laser or electrocautery to destroy the lash follicles. Poor-quality or low-volume tears resulting in reflex overproduction of tears is best treated with regular ocular lubricants.

For Tear Drainage Problems

If the lacrimal puncta within the lids are stenosed, these are dilated and then the punctal opening is enlarged using small fine-tipped scissors ('punctal snip'). Laxity or malposition of the lower lid causing ectropion, so that the punctum does not sit within the lacrimal lake in order to accept tears, requires a lid procedure specific to the underlying eyelid pathology. The most common cause of lacrimal pump dysfunction in the presence of a normal punctal position is lid laxity, which can be repaired with a horizontal lid tightening procedure to reinstate normal lid tension.

The most common mechanical cause of tearing is nasolacrimal duct narrowing. Fortunately, treatment for this, DCR (see the box on page 181), has progressed significantly over the past few years, improving patients' quality of life.[6]

Key Points

- Watery eyes are not a trivial problem for the patient.
- The cause of watery eyes can generally be determined by the family physician.
- It is important to treat a cause of tear overproduction.
- Definitive surgery is available for lower lacrimal system obstruction and lid malposition, and is highly effective, improving quality of life.

Declaration of Interest

None.

A complete list of references can be obtained upon request from the editor.

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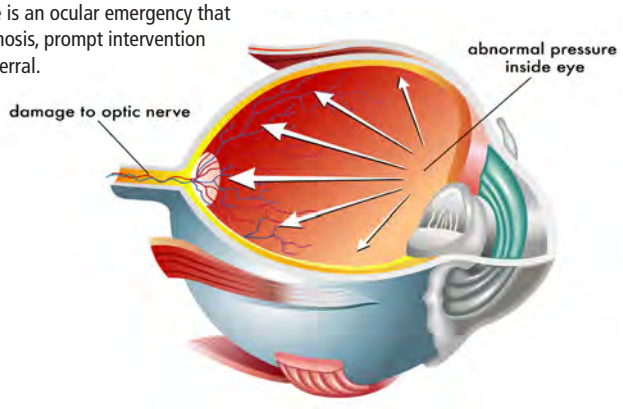
Angle Closure Glaucoma: An Overview

Subhashini Kadappu, MBBS, MS; Allan Bank, FRACS, FRANZCO

Recognition of the symptoms of acute angle closure glaucoma, prompt intervention and appropriate referral are essential to reduce intraocular pressure and prevent permanent visual loss. Progressive circumferential closure of the drainage network of the eye is prevalent in Asians and is being increasingly recognized as a major cause of visual loss.

Acute angle closure is an ocular emergency that requires rapid diagnosis, prompt intervention and appropriate referral.



Glaucoma is the second leading cause of visual impairment worldwide.[1] Angle closure glaucoma accounts for almost half of these cases and is emerging as a leading cause of blindness in Asian countries. With the significant and growing population of Asian origin in Australia, there is an increasing need for awareness of this potentially blinding disease in this country.

Acute angle closure is an ocular emergency that requires rapid diagnosis, prompt intervention and referral to prevent progression and consequent loss of vision. Prophylactic measures are essential to prevent an attack in the fellow eye.

Epidemiology

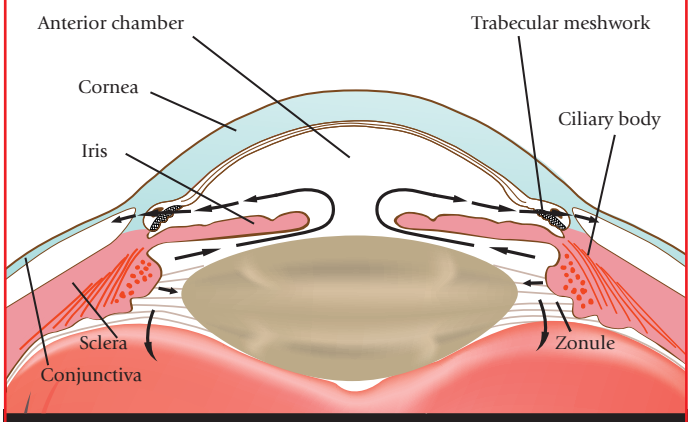
It has been estimated that the prevalence of people with angle closure glaucoma worldwide in 2010 will be 15.7 million.[2] This figure is expected to increase to 21 million by 2020, and of these affected people 5.3 million will be bilaterally blind from the disease.[2] Angle closure glaucoma is more common among South-East Asian and Chinese peoples and Inuits than among Caucasians and Africans. Older people are generally affected (in the sixth to seventh decade of life), and women are affected two to four times more commonly than men.

Terminology

Angle closure glaucoma refers to a disorder of raised intraocular pressure (IOP) due to mechanical blockade, usually by the peripheral iris, of the access to the drainage mechanism of the eye (the trabecular meshwork), with subsequent optic disc and visual field changes.

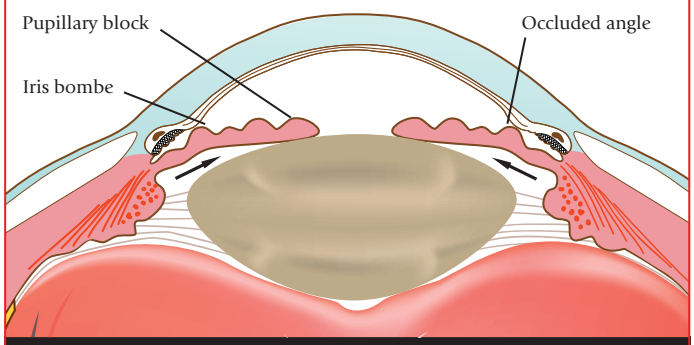
Conceptually, there are five stages in the progression of angle closure glaucoma of unknown cause (primary angle closure glaucoma). These stages range from latent, through subacute, acute and chronic to

Figure 1.



Aqueous circulation in a normal eye (with an anterior chamber of normal depth). Aqueous is secreted by the ciliary body, passes through the pupil into the anterior chamber, and drains through the trabecular meshwork contained in the angle between the cornea and the iris. (Arrows indicate direction of aqueous flow.)

Figure 2.



Angle closure due to pupillary block in an older eye with a shallow anterior chamber and a narrow angle. Pupil dilation can cause the iris to catch on the lens, restricting the normal flow of aqueous from the ciliary body around the lens to the anterior chamber, leading to a pressure differential between the posterior and anterior chambers. As aqueous builds up behind the iris, the peripheral iris bows forward (iris bombe) and occludes the angle, blocking access of the aqueous to the trabecular meshwork and causing the pressure to rise further. The lens (which thickens with increasing age) may also push the peripheral iris forward. (Arrows indicate direction of aqueous flow.)

absolute, the latter referring to the end-stage of untreated disease – an irreversibly blind (no perception of light) eye. In reality, the subacute and acute closure stages merge, and it is this stage that is most commonly encountered in a primary care setting.

Previously, with a lack of standard definitions and criteria, the terms primary angle closure, primary angle closure glaucoma, acute angle closure and acute angle closure glaucoma were used interchangeably. With greater understanding of the epidemiology and revision of the classification, the term primary angle closure glaucoma is now being reserved to indicate the presence of glaucomatous optic neuropathy, with its characteristic visual field defects, in eyes that have signs of primary angle closure.[3] Patients with occludable angles are referred to as primary angle closure suspects.

Chronic angle closure glaucoma refers to the progressive permanent closing of access to the trabecular meshwork, with a gradual rise in IOP and subsequent optic and visual field defects. It is discussed later in this article.

Mechanisms of Angle Closure

In the normal healthy eye, a constant pressure (normal range, 10 to 21 mm Hg) is maintained by the continuous production, circulation and drainage of aqueous humour. Aqueous is secreted by the ciliary body, passes through the pupil into the anterior chamber, and then drains through the trabecular meshwork contained in the angle between the cornea and the iris (Figure 1). Trabecular obstruction consequent to closure (occlusion) of this angle because of iris–lens apposition results in raised IOP and characteristic symptoms and signs – the condition of angle closure.

Racial and hereditary factors and increasing age are important risk factors for angle closure. Several anatomical features lead to anterior chamber crowding and predispose individuals to angle closure. These include shallower anterior chambers, thinner ciliary bodies, anteriorly situated iris–lens diaphragms, and shorter axial eye lengths. Women and Asian people tend to have shallow anterior chambers, as do older people because of the increasing thickness and forward movement of the lens with increasing age. First-degree relatives of people with angle closure are at increased risk because eye shape is often inherited.[4]

Pupillary block (pathologic iris–lens apposition) is probably the most frequent underlying cause of angle closure (Figure 2). In pupillary block, the resistance to aqueous flow from the posterior chamber through the pupil increases and leads to a pressure differential between the posterior and anterior chambers. This pressure gradient causes the peripheral iris to bow forward (iris bombe) and obstruct the trabecular meshwork, with a consequent elevation of IOP. This is most likely to occur when the pupil is mid-dilated. The severe pain in cases of acute angle closure is caused by the very high IOP, as is also the potentially devastating damage to the optic nerve.

Less common mechanisms of angle closure include plateau iris, lens swelling, and ciliary block. Plateau iris is due to anterior insertion of the iris on the ciliary body face,

with the superfluous and crowded iris tissue directly blocking the trabecular meshwork and subsequently increasing IOP. Phacomorphic (or lens shape-related) glaucoma and ciliary block (or malignant) glaucoma are relatively rare. Phacomorphic glaucoma is due to the lens intumescence that may occur in advanced cataracts, with subsequent crowding of the anterior chamber. Ciliary block glaucoma is due to posterior misdirection of aqueous to the vitreous cavity, with increasing vitreous pressure and forward movement of the iris–lens diaphragm leading to angle closure. This has been described after intraocular surgery, in panretinal photocoagulation, after scleral buckling surgery for retinal detachment, and in uveitis.

In anatomically predisposed eyes, the natural response of pupillary dilation to various environmental and chemical stimuli can result in pathologic iris–lens apposition precipitating acute angle closure. Precipitants of an attack include dim illumination, as at night or in cinemas or theatres, and stress or excitement. Several local and systemic drugs may also be precipitants because of their adrenergic, anticholinergic or sometimes idiosyncratic (causing ciliochoroidal effusion) effects.[5] Practitioners prescribing these drugs need to be aware of their potentially blinding side effects (Table 1).

The mechanisms for chronic angle closure are discussed separately later in this article.

Presentation of Primary Angle Closure

Patients with primary angle closure in the acute stage present with periocular pain and headache that is often severe, is usually not relieved by topical anaesthetics, and may radiate in the trigeminal nerve distribution (Table 2). However, it is important to note variability of symptoms in an acute attack; some patients, especially Africans, may have very little pain despite very high IOPs.

Blurred vision and coloured haloes around lights may progress to total visual loss. There may be a past history of transient blurring of vision and haloes around lights, suggesting mild, subacute attacks. In severe cases, systemic symptoms such as nausea, vomiting, sweating and bradycardia may be the main presenting features. The patient is generally unwell, and visual acuity may, although rarely, be reduced to hand movements.

Eye examination of a patient with primary angle closure shows ciliary injection due to congestion of limbal blood vessels. The cornea is usually cloudy due to oedema, and this may limit visualization of the anterior segment. The pupil is mid-dilated and non-reactive (Figure 3). The orbit is hard on digital palpation, compared with the other eye, and tonometry demonstrates raised IOP, which may be as high as 70 mm Hg in some instances.

Examination of the fellow eye is crucial and usually reveals a shallow anterior chamber, with gonioscopy demonstrating narrow angles.

Differential Diagnosis

The clinical features of primary angle closure in the acute stage are generally classic, and the condition should be at the forefront of the list of differential diagnoses because it is sight-threatening and usually reversible. If some features are not typical of primary angle closure, the following differential diagnoses should be considered:

- other causes of acutely raised IOP – traumatic glaucoma, pigmentary glaucoma and inflammatory glaucomas
- other causes of acute, severe ocular pain, red eye and visual loss – keratitis, anterior uveitis, scleritis, endophthalmitis and optic neuritis
- other causes of headache – migraine and tension headache.

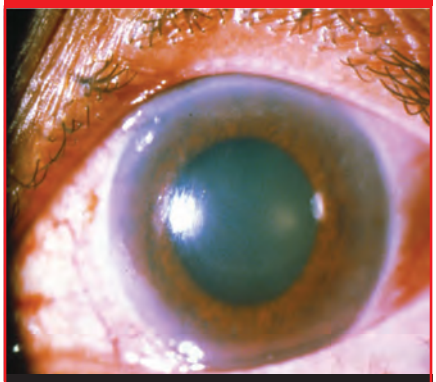
Table 1. Drugs that may precipitate angle closure

- Adrenergic agents – phenylephrine drops, nebulized salbutamol, systemic adrenaline
- Anticholinergics – atropine and homatropine drops, periocular botulinum toxin
- Antihistamines – chlorpheniramine, diphenhydramine
- Antidepressants – amitriptyline, fluoxetine, imipramine, paroxetine, phenelzine
- Selective serotonin reuptake inhibitors – citalopram, venlafaxine
- Sulfa-based drugs – hydrochlorothiazide, sulfamethoxazole, topiramate

Table 2. Symptoms and signs of primary angle closure

Symptoms
Periocular pain
Headache
Blurred vision
Coloured haloes around lights
Nausea, vomiting, sweating, and bradycardia
Signs
Red eye – ciliary injection
Cloudy cornea
Mid-dilated pupil, not responsive to light
Hard orbit

Figure 3.



Mid-dilated pupil and cloudy cornea in primary angle closure.

Primary angle closure is a clinical diagnosis based on a history of ocular pain, blurring of vision, haloes and systemic symptoms (mainly vagal) and the findings of ocular examination. In expert hands, gonioscopy can determine if trabecular blockage is present and gonioscopy itself may break an acute attack. During indentation gonioscopy, the central corneal curvature is altered, pushing aqueous peripherally into the angle recess, and possibly opening the appositionally closed angles.

No definitive laboratory tests or imaging studies are available for angle closure. Ultrasound biomicroscopy and new techniques such as anterior segment optical coherence tomography and use of the scanning peripheral anterior chamber depth analyser may play a role in the screening and management of angle closure.[6]

Management

With prompt diagnosis and treatment, the prognosis for a patient with primary angle closure is excellent. Delays can result in progression to glaucoma, and possibly the devastating consequence of permanent loss of vision.

The early management of primary angle closure is aimed at reducing IOP (and therefore pain) and breaking the acute attack.[7] Once the attack is broken, definitive treatment is performed, usually within 24 to 48 hours, to prevent further attacks.

It is important that patients are aware that first-degree relatives are at increased risk of the condition. Prophylactic laser iridotomy should be considered for relatives found to have shallow anterior chambers.

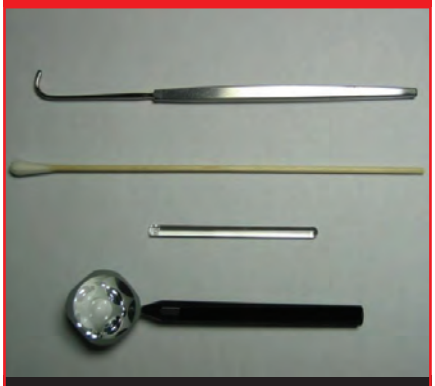
Early Management

Medical Management

The principles of medical management of a patient with an acute attack of primary angle closure are outlined below. Patients should be assessed hourly until the acute attack is broken and then remain under close observation until surgical treatment.

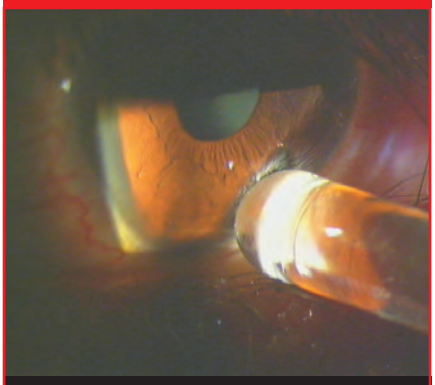
- Urgent referral, day or night, for emergency care – immediate treatment is needed to reduce IOP and save the patient's vision. In the pre-hospital care, the patient should be in the supine position if possible, and the affected eye should not be covered with an eye patch or blindfold (darkness would maintain the pupillary dilation and help perpetuate the attack).
- Posturing of the patient in a supine position – this may allow the lens to fall posteriorly, away from the iris, and may reduce pupillary block.
- To lower IOP, systemic acetazolamide should be given as soon as possible, preferably intravenously (250 to 500 mg over 10 minutes) but otherwise orally (two 250 mg tablets in one dose). Sulfonamide allergy and sickle cell disease or trait should be checked for when using acetazolamide, and urea and electrolytes levels should be monitored. Acetazolamide lowers IOP by reducing the production of aqueous.
- Use of eye drops to lower IOP – eye drops used to lower IOP in cases of open angle glaucoma are often used to help lower IOP in cases of angle closure (off-label use). Timolol, apraclonidine, brimonidine and latanoprost are usually readily available in eye clinics. Topical beta blockers such as timolol 0.5% lower IOP by reducing aqueous production (caution should be taken using timolol in patients with chronic obstructive pulmonary disease or asthma). The topical alpha agonists apraclonidine 0.5% and brimonidine 2 mg/mL lower IOP by both reducing aqueous production and increasing its drainage. The prostaglandin analogue latanoprost lowers IOP by increasing the drainage of aqueous from the eye.
- Use of a miotic – topical pilocarpine can be used to induce pupillary miosis and reverse any pupillary block component (off-label use). Topical pilocarpine 2% is usually stocked and available; pilocarpine 4% can be used. Pilocarpine may be ineffective in inducing miosis in the initial stages of an acute attack because the IOP may be sufficiently high to cause pressure-induced ischaemic paralysis of the iris. Once iris ischaemia is relieved, which is usually when the IOP drops below 50 mm Hg, it is usually effective.
- To reduce the associated ocular inflammation, topical corticosteroids (eg, prednisolone acetate, preferably 1%) can be used.
- Systemic analgesics may be required, as may also anti-emetics (vomiting can drastically increase IOP).
- If the IOP does not reduce with the above treatment, the topical

Figure 4.



Corneal indenting instruments (from top to bottom): squint hook, cotton applicator, glass rod, and gonioscope.

Figure 5.



Method of corneal indentation

medications may be repeated and a systemic hyperosmotic may be added (mannitol 1 to 2 g/kg intravenously over a 45-minute period – a 500 mL bag of mannitol 20% contains 100 g of mannitol; it is essential to consider the patient's cardiovascular and electrolyte status before use). Oral glycerol may be considered in patients who do not have diabetes.

Corneal Indentation

Corneal indentation has been historically described and recently validated as a rapid and effective method in the early management of primary angle closure.[8] This is a simple and non-invasive technique of compressing the inferior cornea using a squint hook, cotton applicator (or the proprietary cotton bud), glass rod, or gonioscope (Figures 4 and 5).

The process of applying pressure to the cornea forces the aqueous into the peripheral anterior chamber and opens the drainage angle. A response is usually seen in three or four cycles of 30 seconds of pressure on and 30 seconds of pressure off the cornea.

Corneal indentation can be performed easily as first-line management in rural settings that have limited access to resources. Not infrequently, corneal indentation without medical treatment can break the acute attack.

Anterior Chamber Paracentesis

Anterior chamber paracentesis has been proposed in the immediate management of primary angle closure because it can dramatically lower IOP and relieve pain.[9] The procedure is, however, invasive and has the potential for iridolenticular trauma, further shallowing of the anterior chamber, iridocorneal touch, corneal endothelial damage and even intraocular infection. It is, therefore, not the procedure of choice, especially in uncooperative patients.

Surgical Treatment

Laser Peripheral Iridotomy

The procedure of laser peripheral iridotomy involves creating an opening in the superior peripheral iris using an Nd:YAG laser (Figure 6). This has the effect of establishing an alternate communication between the posterior and anterior chambers, thus eliminating any pressure differential and thereby preventing further pupillary block. It is usually carried out once the corneal oedema has cleared enough to provide a good view of the iris.

Laser peripheral iridotomy is usually successful in cases where at least 180 degrees of angle is not closed by peripheral anterior synechiae (adhesions of the peripheral iris to the cornea in the anterior chamber angle). Successful laser peripheral iridotomy is creation of a full thickness opening in the peripheral iris; in some instances, the opening may not be full thickness due to iris oedema or poor visibility (corneal haze). If the angle has already closed completely due to synechiae, creation of peripheral iridotomy may not be sufficient.

Prophylactic peripheral iridotomy should be performed in the fellow eye as the risk of acute angle closure if not treated is 40% to 80% in 5 to 10 years.

The procedure is relatively safe but has a few significant complications, the most important being a post-laser spike of IOP (which can be controlled with adequate premedication), iris haemorrhage, and corneal burn. In the long term, there is a small risk of cataract formation.

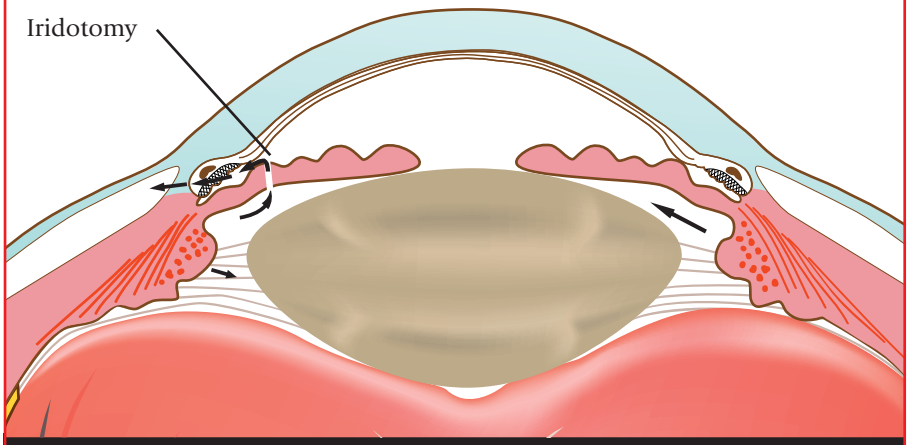
Lensectomy

Lensectomy is known to deepen the anterior chamber, and phacoemulsification with intraocular lens implantation has been advocated for treatment of persistent angle closure and uncontrolled IOP.[10,11] Although it works very effectively, it may not be ideal as an immediate option in eyes with very high IOP.

Chronic Angle Closure Glaucoma

As mentioned earlier, chronic angle closure glaucoma refers to progressive permanent closing of the angle that results in raised IOP and subsequent

Figure 6.



Laser peripheral iridotomy. In an eye with a narrow angle, creating an opening in the superior peripheral iris allows the aqueous to circulate, thereby eliminating any pressure differential and preventing further occlusion of the angle.

optic disc and visual field changes.

Usually a prolonged acute angle closure attack or intermittent subacute attacks lead to progressive formation of peripheral anterior synechiae.

In dark irides, however, a different mechanism of angle closure has been recognized where there is bilateral, progressive, circumferential synechial closure of the trabecular meshwork resulting in a gradual rise in IOP. This has been described previously as creeping angle closure glaucoma. It is prevalent in Asians and is being increasingly recognized as a major cause of visual loss.

Other less common types of chronic angle closure glaucoma are:

- combined mechanism glaucoma – combined open angle and angle closure glaucoma
- mixed mechanism – angle closure due to more than one mechanism
- plateau iris
- miotic-induced – long-term use of miotics resulting in pupillary block.

Laser peripheral iridotomy must be attempted in all cases of chronic angle closure glaucoma because the procedure may open the portion of the angle not closed by synechiae. Argon laser peripheral iridoplasty or trabeculoplasty may be attempted in selected cases. In addition, some patients may need topical antiglaucoma drugs, goniosynechialysis (surgical stripping of peripheral anterior synechiae), or trabeculectomy.

Conclusion

The advent of indentation gonioscopy and laser peripheral iridotomy has led to better understanding of the mechanisms of primary angle closure and considerable advances in its management. Recognition of the symptoms of acute angle closure and urgent referral for treatment is essential to prevent permanent visual loss. Prophylactic laser peripheral iridotomy has emerged as a quick, effective and relatively safe treatment in preventing acute angle closure in eyes at risk.

With the growing Asian population, Australia may see an increasing trend of primary angle closure in the near future and hence there is a greater need for awareness, education and research in this direction.

Declaration of Interests

None.

References

1. Quigley HA. Number of people with glaucoma worldwide. Br J Ophthalmol 1996;80:389–393.
2. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. Br J Ophthalmol 2006;90:262–267.
3. Foster PJ. Advances in understanding primary angle-closure as a cause of glaucomatous optic neuropathy. Community Eye Health 2001;14(39):37–39.
4. Pavlin CJ, Harasiewicz K, Foster FS. Ultrasound biomicroscopy of anterior segment structures in normal and glaucomatous eyes. Am J Ophthalmol 1992;113:381–389.
5. Lachkar Y, Bouassida W. Drug-induced acute angle closure glaucoma. Curr Opin Ophthalmol 2007;18:129–133.
6. Tsai CJ, Tello C, Ritch R. Angle-closure glaucoma update. Focal points. Clinical modules for ophthalmologists, American Academy of Ophthalmology; 2009; 27(6).
7. Ehlers JP, Shah CP, Fenton GL, Hoskins EN, Shelsta HN. The Wills eye manual. 5th ed. Philadelphia: Lippincott Williams and Wilkins; 2008.
8. Masselos K, Bank A, Francis IC, Stapleton F. Corneal indentation in the early management of acute angle closure. Ophthalmology 2009;116:25–29.

A complete list of references can be obtained upon request from the editor.

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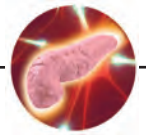
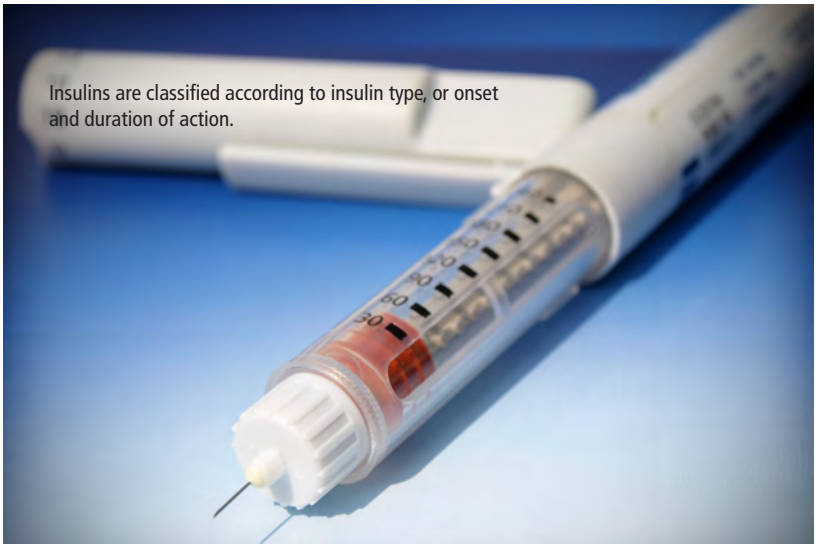
Answers to questions on page 168: 1. F, 2. T, 3. F, 4. T, 5. T



Pharmacological Control of Blood Sugar

Giridhar Tarigopula, MBBS, MRCP(UK); Melanie J Davies, MB, ChB, MD, FRCP

Diabetes is a chronic and progressive metabolic disorder characterized by hyperglycaemia. Good control of blood glucose near physiological limits is vital to reduce long-term microvascular and macrovascular complications of diabetes. This review will look at drugs currently used to optimize blood glucose control and briefly discuss the role of newer therapeutic agents.



Insulins are classified according to insulin type, or onset and duration of action.

Introduction

Diabetes is one of the biggest health challenges faced in the UK. Around 2.6 million people in the country have been diagnosed with the disease and it is predicted that this number will increase to more than 4 million by 2025.[1,2] Optimal and sustained glycaemic control is essential in minimizing long-term complications. Type 1 diabetes (T1DM) is treated with insulin supplemented by educational and psychological support. Type 2 diabetes (T2DM) requires lifestyle interventions, combination drug therapy, and often use of insulin. Current and emerging glucose-lowering therapies for T1DM and T2DM are discussed below.

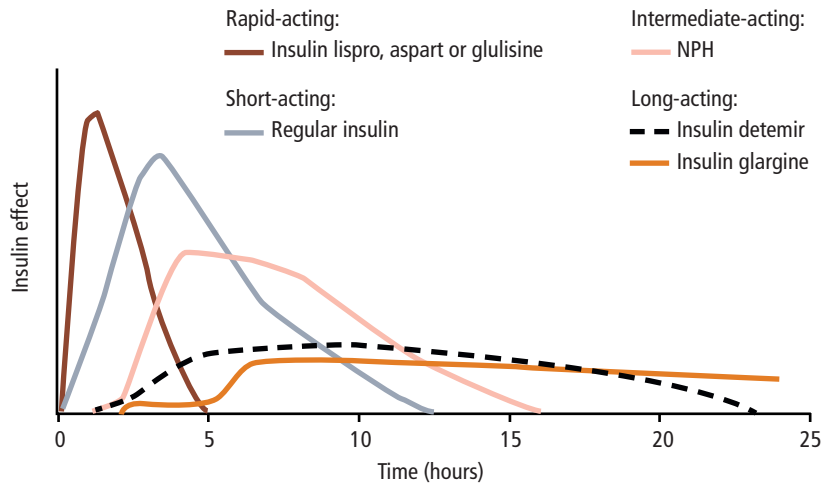
Insulin

Insulin replacement therapy, either regular daily injections by the subcutaneous route or continuously via an insulin pump, is the mainstay of treatment for all patients with T1DM and for individuals with T2DM who do not achieve optimal glycaemic control despite the use of oral agents or non-insulin-based injectable therapies. Hypoglycaemia and weight gain are the major problems associated with glucose-lowering therapies. Insulins are classified according to the preparations as described below or according to onset and duration of action (Figure 1).

Animal Insulins

Animal insulins derived from the pancreatic extracts of animals (eg, cows and pigs) were the earliest insulins used in the treatment of diabetes. However, due to problems with variable rates of insulin absorption, allergic

Figure 1. Types of insulin and duration of action (adapted from Nolte, 2009).



reactions at injection sites and immunogenicity, they have been largely replaced by human insulins and insulin analogues.

Human Insulins

The human insulins were introduced in the early 1980s and are synthetically derived using recombinant DNA technology from yeast and bacteria. They are grouped into short- and intermediate-acting insulins according to their onset and duration of action.

Short-acting Insulins

Short-acting human insulins have a delayed onset of action of 20–30 minutes with duration of action lasting up to 6 hours. Hence, they have to be administered 30 minutes prior to a meal for optimal effect. The prolonged duration of action and variable absorption of this insulin results in early postprandial hyperglycaemia and higher rates of hypoglycaemia.

Intermediate-acting Insulins

Intermediate-acting (basal) insulins (neutral protamine Hagedorn [NPH], lente, ultralente) have an onset of action of 1–2 hours and a peak action of 4–6 hours which can last up to 14 hours. Due to their differing profiles in peaks and duration of action, they are not suitable as a basal insulin in all patients, and nocturnal hypoglycaemia is commonly encountered in clinical use.

Insulin Analogues

Insulin analogues or 'designer insulins' are derived by modifying the structure of the insulin molecule, resulting in improved pharmacokinetics and pharmacological profiles. Based on their onset and duration of action, they are further divided into rapid-acting and long-acting insulin analogues.

Rapid-acting Analogues

Rapid-acting analogues lispro, insulin aspart, glulisine mimic the physiologic action of endogenous prandial insulin release. They can be administered prior, with or just after the meal. They have a peak onset of action of 2 hours and duration of action lasting up to 5 hours. This offers a distinctive advantage in terms of greater freedom and flexibility to inject at variable meal times.

Long-acting Analogues

The long-acting (basal) insulin analogues include glargine and detemir. Their duration of action lasts up to 20–24 hours. These are used as background insulins alongside rapid-acting or short-acting insulins. They have a lower risk of hypoglycaemia especially nocturnal hypoglycaemia when compared with human (basal) insulins. They are also used as add-on therapy to oral hypoglycaemic agents in diabetes patients with inadequately controlled T2DM.

Emerging Ultra-long-acting Insulin (Degludec)

Degludec is a basal ultra-long-acting insulin with duration of action lasting more than 24 hours and is currently being evaluated in clinical trials. It also exhibits significantly lower day-to-day variability and more glucose-stabilizing effect.[3] Clinical trials with patients treated with insulin degludec three times per week showed lower rates of confirmed hypoglycaemia. Reductions in glycated hemoglobin A_{1c} (HbA_{1c}) were similar with once daily or three times weekly dosing (-1.3% and -1.5%) and were comparable with insulin glargine (-1.5%).[4]

Oral Agents in the Treatment of T2DM

Metformin

Metformin belongs to a biguanide class of drugs and works by decreasing gluconeogenesis, reducing hepatic glucose output, and increasing peripheral utilization of glucose by muscles. Metformin is recommended as a first-line drug in the treatment of T2DM

alongside lifestyle interventions. The main side effects are gastrointestinal such as nausea, abdominal discomfort, and diarrhoea. Rare side effects include lactic acidosis. Metformin should be used with caution when renal function is compromised (ie, at estimated glomerular filtration rate [eGFR] ≤ 45 mL/min/1.73 m^2) and is contraindicated with an eGFR ≤ 30 mL/min/1.73 m^2.

"Insulin analogues or 'designer insulins' are derived by modifying the structure of the insulin molecule, resulting in improved pharmacokinetics and pharmacological profiles"

Sulphonylureas

Sulphonylureas are insulin secretagogues and stimulate insulin production by the pancreas. Gliclazide is a short-acting sulphonylurea while glipizide and glimepiride have a longer duration of action. Indications for use include add-on therapy to metformin when blood glucose is poorly controlled, as first-line therapy in non-obese T2DM patients, or when metformin is contraindicated. Side effects include hypoglycaemia and weight gain.

Postprandial Regulators

Postprandial regulator (nateglinide and repaglinide) stimulates insulin release by stimulating the pancreas. They are administered before a meal and reduce postprandial hyperglycaemia. They have a shorter duration of action with a lower incidence of hypoglycaemia. They are usually added to metformin therapy.

Emerging glucose-lowering therapies offer hope, but their safety profile has to be evaluated in the larger clinical trials.

Thiazolidinediones

Thiazolidinediones (TZDs) (pioglitazone and rosiglitazone) belong to the peroxisome proliferator-activated receptors agonist group of drugs. TZDs decrease the peripheral insulin resistance, thereby reducing blood glucose, and can be used singly, added to metformin, sulphonylureas or to a combination of metformin and insulin. TZDs are associated with weight gain and fluid retention and should not be used in patients with heart failure. Studies suggest a link with osteoporosis by these agents and a possible association with cardiac ischaemia by rosiglitazone. Hence, rosiglitazone has recently been withdrawn.[5]

Acarbose

Acarbose inhibits the digestive enzyme α-glucosidase, thus reducing glucose uptake by the intestines resulting in reduction of postprandial glucose. It is commonly added to other oral agents to improve glycaemic control. Common side effects include bloating, flatulence, and diarrhoea.

Dipeptidylpeptidase-4 Inhibitors: (Incretin Enhancers Including Saxagliptin, Sitagliptin and Vildagliptin)

These drugs inhibit the enzyme dipeptidylpeptidase 4, which prolongs the action of endogenous glucagon-like peptide (GLP-1). This augments insulin secretion and decreases glucagon. They are weight-neutral and can be used as monotherapy or as add-on therapy to oral agents. Clinical trials have shown reductions in HbA_{1c} ranging from 0.7% to 0.9% when gliptins were combined with oral agents like metformin or sulphonylureas.[6–8]

Injectable Therapies in T2DM

GLP-1 Agonists: (Incretin Mimetics Including Exenatide and Liraglutide)

The GLP-1 agonists (exenatide and liraglutide) are currently licensed injectable therapies for T2DM. They stimulate the pancreas to release the

Learning objectives

After reading this article, you should be able to:

- understand the different types of insulins used in clinical practice including their duration and actions
- know the oral agents and newer glucose-lowering drugs used in type 2 diabetes
- appreciate that long-term diabetes control can be challenging and that there is an increasing need for newer drugs with good safety profiles and benefits in long-term cardiovascular outcomes.

insulin and decrease the glucagon secretion. They delay gastric emptying, suppress appetite, and promote weight loss. Exenatide has to be injected twice daily in view of its shorter half-life. However, liraglutide is injected once daily. Most studies show reductions of HbA_{1c} of up to 0.9% and weight loss of 3–4 kg with these drugs.[9,10]

Emerging Oral/Injectable Therapies for Type 2 Diabetes

Sodium–Glucose Transporter 2 Inhibitors

This new class of drugs primarily inhibits absorption of glucose in the proximal tubules of kidneys, thus promoting glycosuria and hence decreasing blood glucose levels. Dapagliflozin, canagliflozin, remogliflozin and sergliflozin belong to the class of sodium–glucose transporter-2 inhibitors. Clinical trials with dapagliflozin have demonstrated lowering of HbA_{1c} ranging from 0.5% to 0.9% and weight loss of 2.5–3.4 kg independent of dosage.[11,12] Potential side effects include genitourinary infections and electrolyte disturbances which need evaluation in larger clinical trials.

Long-acting GLP-1 Agonists/ Analogues

These include once-weekly exenatide and albiglutide, which are currently in phase III clinical trials. They have a prolonged duration of action and need to be injected once a week. Clinical trials with once-weekly exenatide have shown reductions in HbA_{1c} of up to -0.95%.[10]

Conclusion

A number of oral and injectable therapies are available to optimize glucose control and prevent disease progression. However, several drug therapies either singly or in combination often fail to achieve blood glucose targets, and their use is limited by undesirable side effects. Emerging therapies offer hope, but their safety profile has to be evaluated in the larger clinical trials. Furthermore, potential benefits in cardiovascular disease require assessment in long-term outcome trials.

Declaration of Interests

Giridhar Tarigopula: None. Melanie J Davies: Professor Melanie Davies has acted as consultant, advisory board member and speaker for Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Servier, BMS and Roche. She has received grants in support of investigator and investigator initiated trials from Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Pfizer, Merck Sharp & Dohme, GlaxoSmithKline and Servier.

References

1. Quality and Outcomes Framework (QOF) 2009.
2. PBS diabetes prevalence model phase 3: key findings. Yorkshire and Humber Public Health Observatory, May 2008.
3. Heise T, Hermanski L, Nosek L, et al. Insulin degludec: less pharmacodynamic variability than insulin glargine under steady state conditions. Poster presentation, Poster 971, presented at European Association for the Studies of Diabetes (EASD), Scientific Sessions 2010, Stockholm; September 2010.
4. Mathieu C, Fulcher G, Rao PV, et al. Insulin degludec, a new generation ultra-long acting insulin, used once daily or 3-times weekly in people with type 2 diabetes: comparison to insulin glargine. Oral presentation no. 4, presented at European Association for the Study of Diabetes (EASD), Scientific Sessions 2010, Stockholm; September 2010.
5. Medicines and Healthcare products Regulatory Agency (MHRA) recommends the withdrawal of rosiglitazone (Avandia, Avandamet) for treatment of diabetes 24.09.10.
6. Hollander P, Li J, Allen E, Chen R; CV181-013 Investigators. Saxagliptin added to a thiazolidinedione improves glycemic control in patients with type 2 diabetes and inadequate control on thiazolidinedione alone. J Clin Endocrinol Metab 2009;94:4810–4819.
7. Charbonnel B, Karasik A, Liu J, Wu M, Meininger G. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone. Diabetes Care 2006;29:2638–2643.
8. Aschner P, Kipnes M, Lunceford J, Mickel C, Davies M, Williams-Herman D. Sitagliptin monotherapy improved glycemic control in the fasting and postprandial states and beta-cell function after 24 weeks in patients with type 2 diabetes. Diabetes 2006;55:A462.
9. Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis. JAMA 2007;298:194–206.
10. Drucker DJ, Buse JB, Taylor K, et al. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. Lancet 2008;372:1240–1250.
11. Zhang L, Feng Y, List J, Kasichayanula S, Pfister M. Dapagliflozin treatment in patients with different stages of type 2 diabetes mellitus: effects on glycaemic control and body weight. Diabetes Obes Metab 2010;12:510–516.
12. List F, Woo V, Morales E, Tang W, Fiedorek FT. Sodium–glucose cotransport inhibition with dapagliflozin in type 2 diabetes. Diabetes Care 2009;32:650–657.

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CME 1 POINT

Investigating the Patient With Cardiac Chest Pain

Jane McCrohon, MBBS, PhD, FRACP; Camilla Wainwright, BA, LLB, MBBS, FRACP; Christopher S Pokorny, MBBS, FRACP, FRCP, FACG—Series Editor

Authoritative advice on the investigation of cardiac chest pain—a common clinical problem— is presented in this article.

Chest pain is one of the most common reasons for presentations to emergency departments. Chest pain due to coronary artery disease is the leading cause of death in Australia, with more than 23,000 deaths attributed to this in 2005 alone.[1] With an estimated 55,000 myocardial infarctions occurring in Australia in 2009,[2] and at an approximate average cost of $281,000 per event,[2] the cost of coronary artery disease is substantial. In addition to this, there are a further 32,452 estimated cases of chest pain not attributed to a myocardial infarct and each chest pain event itself costs $74,000.[2] In addition to enormous financial costs, there is also a high cost of morbidity and mortality.

Defining the nature and possible aetiology of chest pain can pose a diagnostic dilemma for all clinicians, despite there being multiple algorithms to assist in managing these patients. Most investigations are initially performed to explore the possibility of ischaemic heart disease or other high-risk presentations, such as pulmonary embolism. This article predominantly explores the investigation of patients with chest pain in whom the diagnosis of ischaemic heart disease as a cause requires exclusion. It is important, however, to mention that ischaemic symptoms may not present with chest pain, but rather chest pain equivalents, such as dyspnoea on exertion, sweating, or arm, back or jaw discomfort. Up to a third of patients presenting with an acute myocardial infarction may not experience pain at all.[3] Furthermore, 'pain' is a subjective experience, with many patients with myocardial ischaemia describing the experience, as 'discomfort' or 'pressure' rather than pain.

In defining the basis of chest pain, there are a number of investigations from which to choose. These range from the least invasive, such as an electrocardiogram (ECG) or assessment of serum markers for myocardial injury, to more involved tests, such as an exercise stress test, to the more invasive modalities, such as an invasive coronary angiogram. Each has its place and its limitations, and the test of choice for a particular patient is dependent on a number of different considerations.

What remains consistent in any management paradigm is the need for a thorough history and assessment of whether the patient is at low, intermediate or high risk for acute coronary syndromes (ACS). This will in turn determine the most appropriate pathway of investigation and management.

Assessment

Chest pain can be due to cardiac, respiratory, gastrointestinal or musculoskeletal causes. Non-cardiac causes of chest pain include pulmonary embolus, pneumonia, gastritis/peptic ulcer disease and costochondritis. Cardiac causes of chest pain are listed in Table 1. This article focuses on chest pain of a cardiac origin.

Aims of assessment of patients with chest pain are to:

- identify ACS and refer for urgent treatment
- diagnose other sinister causes for chest pain (eg, aortic dissection, pulmonary embolism)
- identify benign causes of chest pain and manage symptoms according to the diagnosis
- recommend risk factor modification in those without a cardiac cause for chest pain but with an adverse risk factor profile.

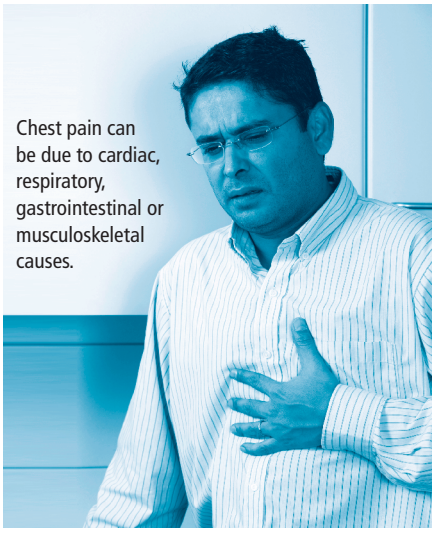
History

The history of all patients presenting with chest pain should include a description of the nature of the pain, the site/location and any precipitating, exacerbating or relieving triggers. It is also important to elicit the duration and timing of the pain, whether the

Table 1. Differential diagnoses for cardiac causes of chest pain

- Acute coronary syndrome
  - ST-segment elevation acute coronary syndrome
  - non-ST segment elevation acute coronary syndrome
  - unstable angina
- Chronic stable angina
- Acute aortic dissection
- Myocarditis/pericarditis
- Aortic stenosis
- Hypertrophic obstructive cardiomyopathy
- Other cardiomyopathies
- Stress-related conditions (eg, takotsubo cardiomyopathy, coronary artery spasm)

pain radiates to another location, such as the arm or the jaw, and whether there are other associated symptoms, such as sweating, nausea or breathlessness, which might point towards ischaemia as the cause. In addition, patients should be asked whether they have experienced the type of pain before and, if so how frequently, and whether they have had prior investigations. A thorough past medical history is important because this can help risk stratify the patient.



Chest pain can be due to cardiac, respiratory, gastrointestinal or musculoskeletal causes.

Characteristics in the pain description that might suggest ACS are:

- central location
- radiating to the left arm and throat
- tight, squeezing, constricting or pressure-like in nature
- more than 5 minutes in duration
- precipitated/exacerbated with exertion (physical or emotional)
- relieved with rest or by nitrate supplements.

The risk factors for ischaemic heart disease include:

- type 2 diabetes
- a history of hypertension
- dyslipidaemia
- increased body mass index
- a significant smoking history
- a family history of premature coronary artery disease.

Physical Examination

In the acute setting of patients presenting with chest pain, examination should focus initially on an assessment of their haemodynamic stability, looking at their blood pressure and heart rate, as well as respiratory rate. Cardiovascular assessment might yield information about whether a patient has a murmur, additional heart sounds, a rub, heave or prominent apex beat. Respiratory examination should focus on whether there is symmetry of the chest on inspiration, whether the breath sounds are vesicular in nature, and whether the lung fields sound clear with no additional wheeze, crepitations or dullness to percussion. Abdominal examination may reveal organomegaly, a pulsatile mass in the situation of an abdominal aortic aneurysm or the presence of ascites in patients with right heart failure. If a patient appears sweaty/clammy with hypotension/hypertension and/or tachycardia, urgent referral to an emergency department is necessary.

It is important to recognize that although an accurate history and thorough examination are very important in the assessment of a patient with chest pain, these alone are not reliable in excluding ACS. Therefore, investigations such as an ECG and blood tests are essential.

Investigations

Routine investigations for any patient who presents with chest pain include a basic ECG. If the ECG is markedly abnormal and there is a high index of suspicion of a cardiac cause of pain (Table 2), urgent referral of the patient to the emergency department should be made. Other basic tests such as a chest radiograph, as well as blood tests, are usually performed in the emergency department but can be done in the outpatient setting if the presentation is not acute and if the patient is not at an intermediate or high risk of ACS.

The box on page 196 provides a brief summary of additional investigations that may be of value in the evaluation and risk stratification of patients with chest pain of a cardiac cause.

ECG

An ECG can diagnose the following:

- ST-segment elevation myocardial infarction (or new left bundle branch block [LBBB]). Patients with this diagnosis require an urgent transfer to hospital for emergency reperfusion (fibrinolysis or primary percutaneous coronary intervention). There are, however, other important causes of ST elevation on an ECG to be aware of (Table 3).
- Acute ischaemic changes (ST-segment depression, T-wave changes). Patients with this diagnosis require an urgent referral to hospital for further investigations.

"It is important to remember that an ECG may be normal in 90% of patients with coronary artery disease"

- Evidence of prior myocardial infarction (pathological Q-waves, a LBBB or if there are persisting T-wave abnormalities). Patients with this diagnosis require a high index of suspicion for urgent referral.
- Arrhythmia with a rapid ventricular response and associated rate-related ischaemia.
- Conduction abnormalities. This may not cause chest pain, but may manifest with other cardiac symptoms of concern, such as syncope or dyspnoea.

It is important to remember that an ECG may be normal in 90% of patients with coronary artery disease.[4]

Chest X-Ray

A chest X-ray can diagnose the following:

- Cardiomegaly. This suggests long-standing cardiac pathology – for example, a cardiomyopathy.
- Widened mediastinum. This may be diagnostic of an acute aortic dissection.
- A globular heart. This may occur with a significant pericardial effusion.
- Upper lobe redistribution of blood vessels/pleural effusion/alveolar oedema. These suggest left ventricular failure.

Table 2. Features associated with high-, intermediate- and low-risk non-ST-segment elevation acute coronary syndrome (ACS)*

High-risk features (> 10% risk)

Presentation with clinical features consistent with ACS and any of the following high-risk features:

- Repetitive or prolonged (> 10 minutes) ongoing chest pain or discomfort
- Elevated level of at least one cardiac biomarker (troponin or creatine kinase-MB isoenzyme)
- Persistent or dynamic electrocardiographic changes of ST-segment depression ≥ 0.5 mm or new T-wave inversion ≥ 2 mm
- Transient ST-segment elevation (≥ 0.5 mm) in more than two continuous leads
- Haemodynamic compromise: systolic blood pressure < 90 mm Hg, cool peripheries, diaphoresis, Killip class > I and/or new-onset mitral regurgitation
- Sustained ventricular tachycardia
- Syncope
- Left ventricular systolic dysfunction (left ventricular ejection fraction < 0.40)
- Prior percutaneous coronary intervention within 6 months or prior coronary artery bypass surgery
- Presence of known diabetes (with typical symptoms of ACS)
- Chronic kidney disease (estimated glomerular filtration rate < 60 mL/min; with typical symptoms of ACS)

Intermediate-risk features (2–10% risk)

Presentation with clinical features consistent with ACS and any of the following intermediate-risk features and who are not meeting the criteria for high-risk ACS:

- Chest pain or discomfort within the past 48 hours that occurred at rest or was repetitive or prolonged (but currently resolved)
- Age > 65 years
- Known coronary heart disease: prior myocardial infarction with left ventricular ejection fraction ≥ 0.40 or known coronary lesion more than 50% stenosed
- No high-risk changes on electrocardiography (see above)
- Two or more of the following risk factors: known hypertension, family history, active smoking or hyperlipidaemia
- Presence of known diabetes (with atypical symptoms of ACS)
- Chronic kidney disease (estimated glomerular filtration rate < 60 mL/min; with atypical symptoms of ACS)
- Prior aspirin use

Low-risk features (< 2%)

Presentation with clinical features consistent with cardiac cause of chest pain without intermediate-risk or high-risk features.

*Reproduced with permission from the Acute Coronary Syndromes Guidelines Working Group. Management of patients with non-ST-segment-elevation acute coronary syndromes. Med J Aust 2006;184:S20–S24.

Additional investigations that may be of value in evaluating patients with cardiac chest pain

Transthoracic echocardiogram

- Able to diagnose significant valvular pathology (eg, aortic stenosis).
- Can identify regional wall motion abnormalities indicating an underlying coronary artery territory, which may have jeopardized blood supply.
- Can exclude pericardial thickening or a pericardial effusion, which may occur in patients with pericarditis.
- Can diagnose type A aortic dissection.

Exercise stress test

- Provides a good non-invasive assessment of a patient's exercise tolerance as well as giving a good guide about exercise-induced cardiac ischaemia and exercise-induced arrhythmias.

Myocardial perfusion scan

- Has a sensitivity of 80% with a negative predictive value of 72% and a positive predictive value of 85%.[5]
- Dipyridamole myocardial perfusion scan is available for those who cannot exercise.

Stress echocardiogram

- Can be performed with an exercise test or using a pharmacological agent, such as dobutamine, in situations where the patient cannot exercise.
- Provides additional information on chamber size and valvular and ventricular function similar to a standard transthoracic echocardiogram.
- Good non-invasive test that has a similar sensitivity and specificity to a nuclear medicine study (positive predictive value of 92% and a negative predictive value of 69% for dobutamine stress echocardiogram).[5]

Computed tomography coronary angiography

- Is an emerging modality to investigate a patient presenting with chest pain.
- Has a high negative predictive value, therefore a result showing no evidence of coronary artery disease is very reassuring.
- Can also identify non-coronary cardiac pathologies as well as incidental non-cardiac abnormalities that may be the underlying reason for the patient's presentation.

Coronary angiogram

- Is the current gold-standard investigation to identify coronary artery disease in patients who present with acute coronary syndrome.
- Allows visualization of the lumen of the coronary arteries to identify possible narrowed segments responsible for ischaemia or even complete acute occlusion in the case of an acute infarct or a chronic occlusion.
- An assessment can be made at the time of angiography whether revascularization is necessary and whether it can be done percutaneously or whether referral of the patient for coronary artery bypass grafting is appropriate.

Cardiac magnetic resonance imaging

- Is not available in all centres but is a very useful tool that has the advantage of not using ionizing radiation but providing excellent temporal and spatial resolution.
- Has the ability to assess the pericardium.
- Evaluates ventricular function.
- Allows excellent tissue characterization.
- The diagnostic test of choice if myopericarditis is suspected.
- Can localize the region of acute coronary syndrome or identify underlying coronary ischaemia with a perfusion modality.
- Recommended in patients with congenital heart disease or aortic disease, especially for serial evaluation.

Table 3. Differential diagnoses for ST elevation on electrocardiogram

- Acute ST-segment elevation acute coronary syndrome
- Pericarditis
- Early repolarization
- Left ventricle aneurysm post infarction

Blood Tests

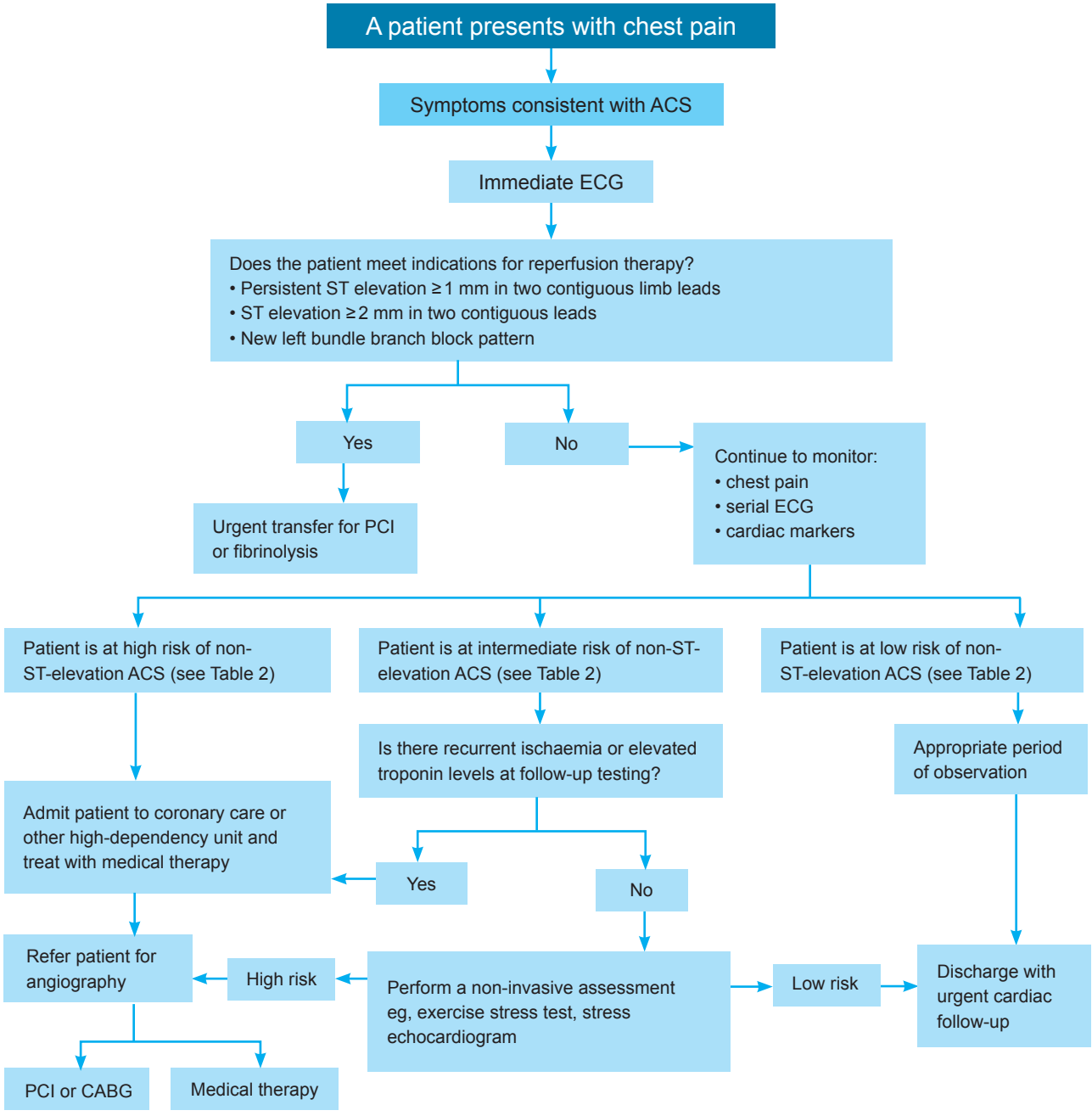
Results of blood tests may suggest the following:

- Raised creatine kinase-MB isoenzyme and cardiac troponin I levels. This is diagnostic of acute myocardial damage.
- Severe anaemia detected by a full blood count. This may provoke angina. A raised white blood cell count may indicate infection.
- Raised inflammatory markers, erythrocyte sedimentation rate and C-reactive protein levels. This may lend evidence for an inflammatory state such as myopericarditis or an underlying infection.
- Elevated liver function tests. This may identify a diagnosis of acute cholecystitis/cholelithiasis.

Referral for Cardiac Diagnostic Testing

The method and timeline for continued assessment of a patient with chest pain of potential ischaemic origin may occur in the inpatient or outpatient setting. Any patient with acute ECG changes, continuing potentially ischaemic pain or symptoms suggesting possible ACS will more than likely require admission and urgent review in hospital. (The case study on page 198 outlines the assessment of a man with persisting

Investigating a patient presenting to the emergency department with chest pain of possible cardiac origin*



* Based on the National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand 'Guidelines for the management of acute coronary syndromes 2006'.[6]

ACS = acute coronary syndrome; CABG = coronary artery bypass grafting; ECG = electrocardiogram; PCI = percutaneous coronary intervention.

Case study. A man with persisting symptoms of chest pain

A 51-year-old man with a 6-month history of intermittent chest pain presented to his local doctor for review. He had a history of hypertension but had achieved good blood pressure control on antihypertensive medication. He had no other significant risk factors for coronary artery disease. His episodes of chest pain had been short-lived and had predominantly occurred postprandially with no associated symptoms of dyspnoea or sweating. The chest pain usually subsided spontaneously within 10 to 15 minutes. An electrocardiogram showed normal sinus rhythm and some routine blood tests did not reveal any abnormality except that his fasting lipid profile was mildly abnormal.

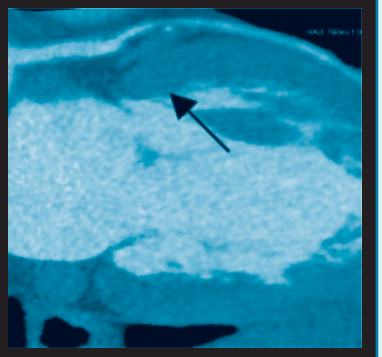
The patient's symptoms of chest pain persisted over the following week and as they were somewhat atypical, a gastroenterologist's opinion was sought. An endoscopy demonstrated gastritis and Barrett's oesophagus, and he was commenced on therapy for this. However, he continued to get intermittent epigastric/chest pain and started to experience some mild exertional dyspnoea, which was a new feature. He was referred for an exercise stress test, and an appointment was made for cardiology review thereafter.

Unfortunately, during the stress test, the patient was only able to exercise for 4 minutes of the Bruce protocol because he was limited by knee pain due to a recent injury. Therefore, the stress test was submaximal. After reviewing the patient and given that there had been no progression of his symptoms and that he had an intermediate probability of coronary artery disease, his cardiologist referred him for a computed tomographic (CT) coronary angiogram.

The CT coronary angiogram demonstrated a critical stenosis in his proximal left anterior descending coronary artery and two tandem stenoses in his first diagonal branch, with disease in his left circumflex artery as well (Figures 1 and 2). He then proceeded to an invasive coronary angiography and a successful percutaneous coronary intervention with stents deployed to his left anterior descending coronary artery and diagonal arteries (Figures 3 and 4).

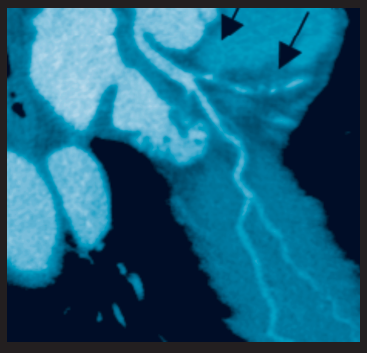
The patient was reviewed several months later, and he reported feeling well with no residual symptoms. He had also resumed regular exercise.

Figure 1.



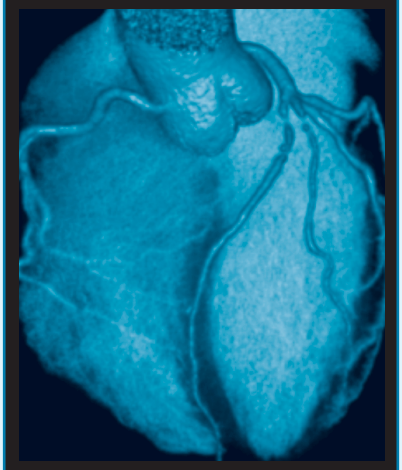
CT coronary angiogram demonstrating significant soft plaque (> 80% stenosis) in the proximal left anterior descending coronary artery (arrow).

Figure 2.



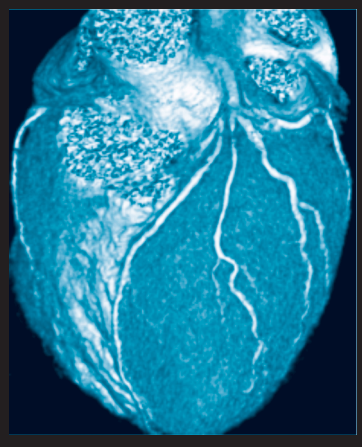
CT coronary angiogram multiplanar reconstruction demonstrating the left anterior descending coronary artery and diagonal branch (arrows) with significant soft plaque causing severe obstructive stenoses.

Figure 3.



Three-dimensional coronary tree reconstruction showing the severe obstructive stenoses.

Figure 4.



Three-dimensional reconstruction showing the anterior aspect of the heart with the left anterior descending artery and diagonal branches.

The management of the patient with chest pain is a complex issue.

symptoms of chest pain.) A percentage of these patients will have troponin elevation excluded and may undergo a basic risk stratification process, allowing their discharge or subsequent hospitalization.

A general flowchart outlining investigations for patients referred to the emergency department with chest pain of possible cardiac origin is shown on page 197.[6] Once a patient has been diagnosed with ACS, the timing of referral for angiography is dependent on whether the patient is at high, intermediate or low risk.

The Future

The management of the patient with chest pain is a complex issue. Importantly, our health system and clinical practice is likely to be shaped in the years ahead by economic and efficiency concerns, along with technological advances and information emerging from randomized controlled trials, which are designed to evaluate the best algorithm for patients presenting with cardiac chest pain.

Conclusion

It is important to identify early those patients with typical sounding chest pain or significant risk factors for ischaemic heart disease. Any patient with ST-segment elevation ACS should be referred for urgent cardiac catheterization, or fibrinolytic therapy if there is likely to be a delay in catheterization or there is no facility available for percutaneous coronary intervention.

Once a patient has been diagnosed with a non-ST-segment elevation ACS, he or she should be risk stratified as high, intermediate or low risk and referred for investigations appropriately.

Declaration of Interest

None.

References

1. Australian Government, Australian Institute of Health and Welfare. Available online at: http://www.aihw.gov.au/cvd/documents/ischaemic _heart_diseases_05.xls (accessed October 2010).
2. Access Economics. The economic costs of heart attack and chest pain (Acute Coronary Syndrome). 2009. Available online at: http://www.accesseconomics.com.au/publicationsreports/showreport.php?id=204&searchfor=2009&searchby=year (accessed October 2010).
3. Canto JG, Shlipak MG, Rogers WJ, et al. Prevalence, clinical characteristics, and mortality among patients with myocardial infarction presenting without chest pain. JAMA 2000;283:3223–3229.
4. Norell M, Lythall D, Coghlan G, et al. Limited value of the resting electrocardiogram in assessing patients with recent onset chest pain: lessons from a chest pain clinic. Br Heart J 1992;67:53–56.
5. San Román JA, Vilacosta I, Castillo JA, et al. Selection of the optimal stress test for the diagnosis of coronary artery disease. Heart 1998;80:370–376.
6. Aroney CN, Aylward P, Kelly AM, Chew DPB, Clune E. National Heart Foundation of Australia & Cardiac Society of Australia and New Zealand. Guidelines for the management of acute coronary Syndromes. Med J Aust 2006;184;S1–S32.

In summary

- The diagnosis and investigation of the patient with chest pain can be challenging.
- The early identification of a patient with acute coronary syndrome or other sinister causes for chest pain, such as aortic dissection or pulmonary embolism, is important to allow early intervention and treatment.
- Risk stratification of any patient with chest pain aids in the decision for investigations.
- Patients without cardiac causes for chest pain but with adverse risk factor profiles can be recommended for risk factor modification.

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CME Questions

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CME 1 POINT

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CME Article:
Investigating the Patient With Cardiac Chest Pain

Please indicate on your answer sheet whether the following statements are True or False.

1. **A thorough past medical history of a patient presenting with chest pain is helpful for cardiac cause risk stratification.**
2. **If a patient with chest pain appears sweaty or clammy and has either hypotension or hypertension, and/or tachycardia, they should be immediately referred to an emergency department.**
3. **The presence of acute coronary syndrome (ACS) can be excluded based on the results of history and physical examination assessments alone.**
4. **A basic electrocardiogram is a routine investigation for any patient presenting with chest pain.**
5. **Chest X-rays and blood tests can be performed in the outpatient setting if the presentation is not acute and the patient is at low risk of ACS.**
6. **Patients with ST-segment elevation ACS should be referred for urgent percutaneous coronary intervention (PCI) or fibrinolysis.**
7. **Patients with non-ST-segment elevation ACS are not likely to require PCI or medical therapy.**
8. **Patients with non-ST-segment elevation ACS, together with sustained ventricular tachycardia, should be classified as high risk.**
9. **Patients with high-risk non-ST-segment elevation ACS should be immediately admitted to a high dependency unit for medical treatment.**
10. **Patients with low-risk non-ST-segment elevation ACS can be discharged without observation or follow-up.**

CME 1 POINT

Hypertension—Treating to Target

Faline S Howes, BMedSci, MBBS(Hons), MPubHlth, FRACGP; Mark R Nelson, MBBS(Hons), MFM, FRACGP, FAFPHM, PhD

The choice of antihypertensive agent is determined by its effectiveness, and its indications and contraindications for the individual patient. Whichever agent is used, it is important to treat to goal.

Hypertension is the most frequently managed problem in Australian general practice.[1] The prevalence rate in the adult population is 29%.[2] The benefits of blood pressure lowering have been detailed in numerous randomized, placebo-controlled trials and meta-analyses.[3] However, hypertension is still described as the most important health problem that is suboptimally managed.

In the Australian Diabetes, Obesity and Lifestyle (AusDiab) study, treatment for hypertension was justified in 54% of patients not treated.[2] Of those taking antihypertensive medication, only 40% had reached target blood pressure readings (defined as < 140/90 mm Hg). Blood pressure control rates can therefore be substantially improved.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) and the Controlled Onset Verapamil Investigation of Cardiovascular Endpoints (CONVINCE) study achieved target blood pressure levels in 66% and 70% of patients, respectively.[4,5] Hence higher rates of blood pressure control are achievable.

Failure to reach blood pressure targets may be due to the patient, the GP or systems issues. This article discusses some of the reasons why blood pressure targets set by the National Heart Foundation's guidelines are not reached, what the target blood pressure readings are, and ways in which these targets may be achieved.[6]

Why Are We Not Reaching Blood Pressure Targets?

A qualitative study has investigated the barriers to initiating medication and treating elevated blood pressure to target levels in general practice.[7] In this study, the main barrier pre-

Failure to reach blood pressure targets may be due to the patient, the GP or systems issues.

venting or delaying diagnosis reported by GPs was a lack of confidence in the accuracy and representativeness of blood pressures recorded in their clinic. The other main barriers were the time-poor nature of general practice and perceived patient attitude. The fact that multiple readings are needed over several visits imposed some difficulties – for example, in patients who were infrequent attendees or were not interested in their blood pressure or saw a different doctor each time they attended. Initiation of treatment was often hampered by patient unwillingness to take medications.

The study also found that the decision to treat to target was clouded by doctors' fear of adverse events (particularly in the elderly) clinical inertia and perceived patient attitude. Adopting a patient-centred care approach and distrust of the evidence underlying the management of hypertension had a pervasive impact.

In this study, difficulties associated with initiating and treating to target were often discussed together, but overall treating to target was viewed as being more difficult. Looking at the study results from a treating to target perspective only, the barriers that prevented optimal management of hypertension were perceived patient attitude, GP attitude and systems issues.

Table 1. Blood pressure treatment targets in adults*

Patient group	Target (mm Hg)
Patients with proteinuria >1 g/day (with or without diabetes)	<125/75
Patients with associated condition(s) or end organ damage:† • coronary heart disease • diabetes • chronic kidney disease • proteinuria (>300 mg/day) • stroke/transient ischaemic attack	<130/80
Patients with none of the above	<140/90 or lower if tolerated

*Adapted with permission from *Guide to management of hypertension 2008. Updated September 2010* (in production). Copyright National Heart Foundation of Australia.[6]

†Specific lower blood pressure targets have not been established for other high-risk groups (eg, those with peripheral arterial disease, those with familial hypercholesterolaemia or those at high absolute risk of cardiovascular disease) owing to the current lack of evidence from clinical trials. Targets will be set when evidence becomes available.

"Patients with high absolute cardiovascular risk and elevated blood pressure need to be treated to recommended target blood pressures"

Perceived Patient Attitude

GPs believe that patients often fail to take responsibility for their own health and resist making necessary lifestyle changes. Cost, access and adherence are also issues.

GP Attitude

GPs undertook an informal risk–benefit analysis whereby they weighed up what they were trying to achieve against what the patient wanted. The witnessing of drug attributed side effects, particularly in the elderly, made GPs more risk averse.

Systems Issues

GPs felt that there needed to be greater access to specialist care and home and ambulatory blood pressure monitoring, and improved Medicare support for the management of complex hypertension.

How Can We Reach Blood Pressure Targets?

Patients with high absolute cardiovascular risk and elevated blood pressure need to be treated to recommended target blood pressures (Table 1), otherwise they will have a significant residual adverse risk.

Multiple large studies have shown that all antihypertensive medications have similar efficacy.[8] Therefore, medication choice after initiation is driven by the individual patient's response, co-morbidity (Table 2) and the possible combinations of antihypertensive agents (Table 3).[9,10]

To facilitate a successful and sustainable treatment regimen, the lowest recommended dose of the selected drug should be started and then reviewed after 6 weeks.

Table 2. Choice of antihypertensive agent in patients with co-morbid and associated conditions*

Condition	Potentially beneficial	Potentially harmful	
		Caution	Contraindicated
Angina	Beta blockers (except oxprenolol, pindolol), CCBs, ACE inhibitors		
Atrial fibrillation	Remodelling: ACE inhibitors, angiotensin II receptor antagonists[†] Rate control: verapamil, diltiazem, beta blockers		
Asthma/COPD		Cardioselective beta blockers (eg, atenolol, metoprolol): use cautiously in mild/moderate asthma/COPD only	Beta blockers (except cardioselective agents)
Bradycardia, second- or third-degree atrioventricular block			Beta blockers, verapamil, diltiazem
Depression		Beta blockers, clonidine, methyldopa, moxonidine	
Gout	Losartan	Thiazide diuretics	
Heart failure	ACE inhibitors, angiotensin II receptor antagonists,[†] thiazide diuretics, beta blockers[‡] (bisoprolol, carvedilol, metoprolol controlled release), spironolactone	CCBs (especially verapamil, diltiazem)	Alpha blockers in aortic stenosis Beta blockers in uncontrolled heart failure
Post myocardial infarction	Beta blockers (except oxprenolol, pindolol), ACE inhibitors, eplerenone		
Pregnancy	This section is currently under review[§]		
Chronic kidney disease	ACE inhibitors, angiotensin II receptor antagonists[†]		
Tight bilateral renal artery stenosis (unilateral in a patient with solitary kidney)		ACE inhibitors, angiotensin II receptor antagonists	
Post stroke	ACE inhibitors, angiotensin II receptor antagonists, low-dose thiazide-like diuretics		
Type 1 or type 2 diabetes with proteinuria or microalbuminuria	ACE inhibitor, angiotensin II receptor antagonists[†]	Beta blockers, thiazide diuretics[¶]	

ACE = angiotensin-converting enzyme; CCB = calcium channel blocker.

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[†]Careful monitoring of kidney function is required if a combination of ACE inhibitors and angiotensin II receptor antagonists are used.

[‡]Particular beta blockers are now indicated for the treatment of heart failure. See the Heart Foundation's Guidelines for the prevention, detection and management of chronic heart failure in Australia, 2006 (available at www.heartfoundation.org.au).

[§]This information is currently being reviewed by the Heart Foundation. Please visit www.heartfoundation.org.au/Professional_Information/Clinical_Practice/Hypertension for updated information.

[¶]When used in combination with an ACE inhibitor, may be beneficial in type 2 diabetes.

At this stage, if the patient is unable to tolerate the medication or if it is deemed to be ineffective, the patient should be switched to an antihypertensive drug from a different class. If there has been a partial response but target blood pressure has not been reached, rather than increasing the dose of the first agent, a second agent from a different pharmacological class should be added at a low dose. This approach minimizes adverse events and maximizes efficacy. The effective tolerated medications should be titrated up until target blood pressure is reached; however, additional medications may need to be added to achieve this.

Lifelong medication is usually required because age is the most important determinant of adverse risk. Once blood pressure has been stabilized, the interval between visits can be lengthened – for example, patients should be reviewed every 3 months for the next 12 months, and then 6 monthly thereafter while their blood pressure remains stable.

Behavioural modification is an important component of treatment and, if significant lifestyle changes are made and maintained, patients may be able to stop or reduce drug therapy.[11] Lifestyle interventions remain the cornerstone of hypertension management.

Table 3. Recommended and discouraged combination therapy for the management of elevated blood pressure*[9,10]

First drug	Additional drug	Recommendation
The most effective combination (based on the best available evidence)		
ACE inhibitor or angiotensin II receptor antagonist†	CCB	Particular role in patients with diabetes or lipid abnormalities
Other effective combinations		
ACE inhibitor or angiotensin II receptor antagonist†	Thiazide diuretic	Particular role in patients with heart failure or post stroke
	Beta blocker	Recommended post myocardial infarction or in patients with heart failure
Beta blocker	Dihydropyridine CCB	Particular role in patients with coronary heart disease
Thiazide diuretic	CCB	
	Beta blocker	Not recommended in patients with glucose intolerance, metabolic syndrome or established diabetes
Combinations to avoid		
ACE inhibitor or angiotensin II receptor antagonist	Potassium-sparing diuretic	Avoid combination owing to risk of hyperkalaemia
Verapamil	Beta blocker	Avoid combination owing to risk of heart block
ACE inhibitor	Angiotensin II receptor antagonist	In a large trial,[9] combination therapy did not reduce cardiovascular death or morbidity in patients with vascular disease or diabetes, but increased the risk of hypotensive symptoms, syncope and renal dysfunction‡

ACE = angiotensin-converting enzyme; CCB = calcium channel blocker.

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†ACE inhibitors and angiotensin II receptor antagonists have been shown to be equally efficacious in the prevention of combined end points of cardiovascular disease death, myocardial infarction, stroke and heart failure admissions in patients at high risk owing to past cardiovascular events.

‡Combination therapy reduces proteinuria. Trials to determine the effect of combination therapy on progression of renal disease in subjects with proteinuria are under way.[10]

Combination Therapy

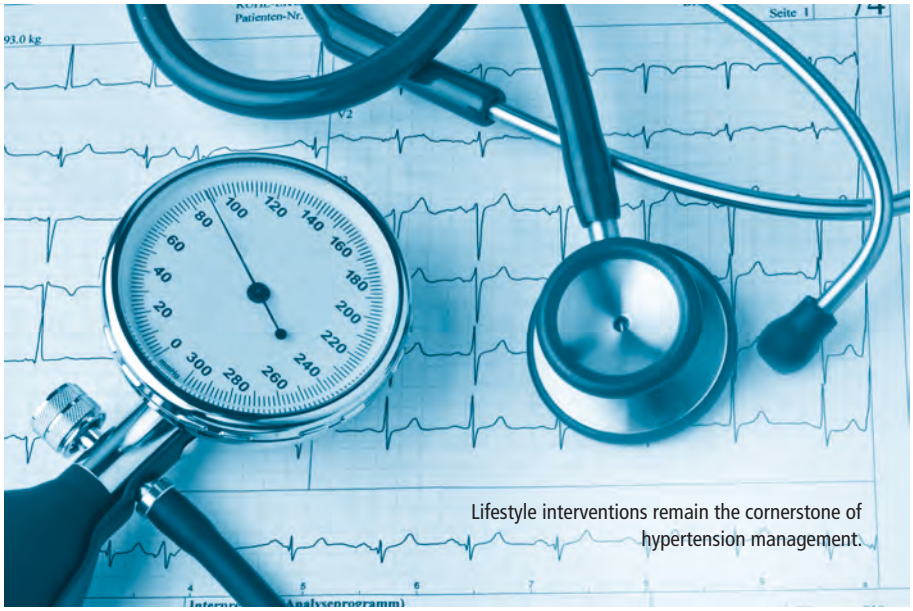
About 60% of patients with elevated blood pressure will not achieve blood pressure targets with one medication alone.[6] Therefore, most patients will require a combination of two or more medications to achieve adequate blood pressure control.

Effective drug combinations for hypertension are shown in Table 3. The angiotensin-converting enzyme (ACE) inhibitor and calcium channel blocker combination has been given precedence due to the results of the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) trial.[12] If required, other useful agents include, for example, alpha blockers and centrally-acting agents. Each change in treatment needs to be trialled for at least 6 weeks.

Still Not at Target?

If target blood pressure is not reached despite maximal doses of at least two appropriate agents after a reasonable period, then the following factors outlined below should be considered.

"About 60% of patients with elevated blood pressure will not achieve blood pressure targets with one medication alone"



Lifestyle interventions remain the cornerstone of hypertension management.

Medication Adherence

- Has the patient ceased medication owing to side effects or cost?
- Could the patient change to a long-acting preparation with once-daily administration?
- Could the patient change to a combination preparation to enhance adherence?
- Would the patient benefit from the use of adherence aids (eg, dosette boxes, Webster packs, written instructions or patient education materials)?

Other Substances That May Increase Blood Pressure

- Is the patient taking a prescribed medication (eg, NSAIDs or prednisolone)?
- Is the patient taking an over-the-counter (eg, NSAIDs) or a complementary medication (eg, ginseng, St John's Wort)?
- Is alcohol, recreational drugs or other drug use (including caffeine, liquorice) an issue?
- Does the patient have a high salt intake (particularly in those taking ACE inhibitors or angiotensin II receptor antagonists)?

Adverse Lifestyle Factors

- Can the patient be motivated to take greater responsibility for his or her health and become a partner in management decisions?
- Can the patient increase physical activity or reduce kilojoule intake (if appropriate)?

Systems Issues

- Are there any other social or economic barriers that are impacting negatively on the patient's health?
- Would the patient benefit from a Home Medicines Review?
- Is a practice recall or reminder system appropriate to assist in management?

Therapeutic Inertia

- Do you need to increase a current agent or add another agent?

Measurement Issues

- Could there be a white coat effect? Home blood pressure monitoring

should be encouraged, if appropriate, or ambulatory blood pressure monitoring considered.

- Is there a blood pressure measurement artifact (eg, inappropriate cuff size)?

Secondary Hypertension

- Does the patient have chronic kidney disease, primary aldosteronism, phaeochromocytoma or renovascular disease?
- Could the patient have obstructive sleep apnoea?
- Is the patient volume overloaded (in particular, chronic kidney disease should be ruled out)?
- Would the patient benefit from referral to a specialist?

Achieving recommended blood pressure target levels in the very elderly may be difficult

Can We Achieve Blood Pressure Targets in the Elderly?

It is recognized that achieving recommended blood pressure target levels in the very elderly may be difficult because of their altered physiological responses, co-morbidity and polypharmacy, with the potential for side effects and medication interactions. The elderly are the most at risk of adverse cardiovascular events.

Randomized, controlled trials have demonstrated that drug therapy is just as effective in advanced age. The most recent study to show this was the Hypertension in the Very Elderly Trial (HYVET).[13] This placebo-controlled trial (mean age, 83.6 years) showed a 39% reduction in the rate of death from a stroke, a 21% reduction in the rate of death from any cause, a 23% reduction in the rate of death from cardiovascular causes, and a 64% reduction in the rate of heart failure in patients taking active treatment versus placebo.

Most importantly, the HYVET study reported fewer serious adverse events in the active treatment group, and preliminary analyses revealed no increase in postural hypotension. If symptoms suggest postural hypotension, but it is not demonstrable in the clinic, it should be confirmed with ambulatory blood pressure monitoring. If confirmed, treatment should be based on the standing blood pressure. In the elderly, isolated elevated systolic blood pressure is more prevalent owing to large vessel stiffness associated with ageing. In these circumstances, a calcium channel blocker or diuretic-based treatment regimen is recommended.

Conclusion

Drug therapy is warranted in patients with a high risk of adverse cardiovascular events together with appropriate behavioural modification. All groups of blood pressure lowering drugs have similar efficacy, but specific agent recommendations are made based on the patient's characteristics. It is important to treat to goal whichever agent is used. Most often, this requires more than one drug to reduce fatal and nonfatal cardiovascular events.

References

1. Britt H, Miller GC, Charles J, Henderson J, et al. General practice activity in Australia 2007–08. General practice series no. 22. Cat. no. GEP 22 Canberra: AIHW; 2008.
2. Briganti EM, Shaw JE, Chadban SJ, et al. Untreated hypertension among Australian adults: the 1999–2000 Australian Diabetes, Obesity and Lifestyle Study (AusDiab). Med J Aust 2003;179:135–139.
3. Mancia G, De Backer G, Dominiczak A, et al. Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2007;25:1105–1187.
4. Furberg CD, Wright JT, Davis BR, et al. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 2002;288:2981–2997.
5. Black HR, Elliott WJ, Grandits G, et al. Principal results of

In summary

- The decision to treat elevated blood pressure with drugs should be determined by an individual's high absolute risk of having an adverse cardiovascular event.
- Not treating to target therefore means that such individuals are at high residual risk.
- Failure to reach blood pressure targets may be due to the patient, the GP or systems issues.
- The choice of antihypertensive agent is determined by its effectiveness, and its indications and contraindications for the individual patient.
- Most patients will require two or more drugs to reach their target blood pressure.
- Drug therapy should always be accompanied by appropriate advice on behavioural modifications.

the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial. JAMA 2003;289:2073–2082.

6. National Heart Foundation of Australia (National Blood Pressure and Vascular Disease Advisory Committee). Guide to management of hypertension 2008. Updated September 2010 (in production).

7. Howes F, Hansen E, Williams D, Nelson M. A qualitative study of barriers to diagnosing and managing hypertension in Australian general practice. Aust Fam Physician 2010;39:511–516.

8. Neaton J, Grimm RJ, Prineas R, et al. Treatment of Mild Hypertension Study: final results. JAMA 1993;270:713–724.

9. The ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008;358:1547–1559.

10. Parving H, Brenner BM, McMurray JJV, et al. Dual renin-angiotensin system blockade and kidney disease. J Am Coll Cardiol 2009;54:278–279.

11. Nelson MR, Reid CM, Muir T, Krum H, Ryan P, McNeil JJ. Predictors of normotension on withdrawal of antihypertensive drugs in second Australian national blood pressure study cohort. BMJ 2002;325:815–817.

12. Kjeldsen SE, Jamerson KA, Bakris GL, et al. Avoiding Cardiovascular events through COMbination therapy in Patients LIving with Systolic Hypertension investigators. Predictors of blood pressure response to intensified and fixed combination treatment of hypertension: the ACCOMPLISH study. Blood Press 2008;17:7–17.

13. Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. N Engl J Med 2008;358:1887–1898.

Declaration of Interests

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CME Article:
Hypertension—Treating to Target

Please indicate on your answer sheet whether the following statements are True or False.

1. **Barriers to optimal hypertension management are perceived patient attitudes, GP attitudes and system issues such as better access to specialist care or home monitoring.**
2. **Blood pressure treatment targets for patients with proteinuria > 1 g/day with or without diabetes should be less than 125/75 mm Hg.**
3. **High absolute cardiovascular risk determines patients' need to be treated for elevated blood pressure.**
4. **A successful and sustainable treatment regimen should begin with the highest tolerated dose of the selected drug and then reviewed after 6 weeks.**
5. **Patients may discontinue treatment once target blood pressure is achieved because age is not an important determinant of adverse risk.**
6. **Lifestyle interventions are a negligible component of hypertension management.**
7. **Most hypertensive patients require multiple drug therapy to control their blood pressure.**
8. **Substances that may increase blood pressure include prescribed or over-the-counter medications, alcohol, drugs and high salt intake.**
9. **Secondary hypertension could be due to renal disease or obstructive sleep apnoea.**
10. **Treating to goal blood pressure is only important when using some medications.**