HYPERTENSION IN ADULTS | TICAGRELOR | MULTIPLE SCLEROSIS

Best Practice

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Issue 54 August 2013

Managing "red eye"

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ACKNOWLEDGEMENT
We would like to acknowledge the following people for their guidance and expertise in developing this edition:
Peter Grimmer, Wellington
Dr Rosemary Ikram, Christchurch
Dr Logan Mitchell, Dunedin
Dr Mark Webster, Auckland
Dr Ernie Willoughby, Auckland

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Best Practice

Issue 54 August 2013

Best Practice Journal (BPJ)
ISSN 1177-5645 (Print)
ISSN 2253-1947 (Online)

BPJ is published and owned by bpac^{nz} Ltd
Level 8, 10 George Street, Dunedin, New Zealand.

Bpac^{nz} Ltd is an independent organisation that promotes health care interventions which meet patients' needs and are evidence based, cost effective and suitable for the New Zealand context.

We develop and distribute evidence based resources which describe, facilitate and help overcome the barriers to best practice.

Bpac^{nz} Ltd is currently funded through contracts with PHARMAC and DHB Shared Services.

Bpac^{nz} Ltd has five shareholders: Procare Health, South Link Health, General Practice NZ, the University of Otago and Pegasus Health.

Printed in New Zealand on paper sourced from well-managed sustainable forests using mineral oil free, soy-based vegetable inks

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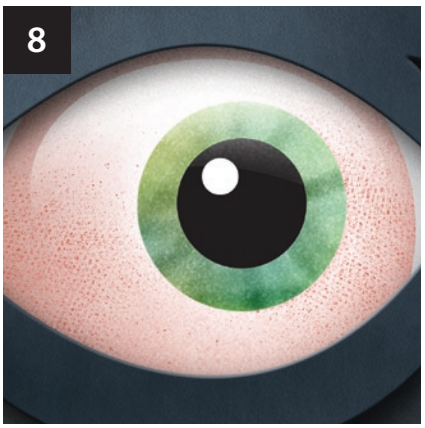

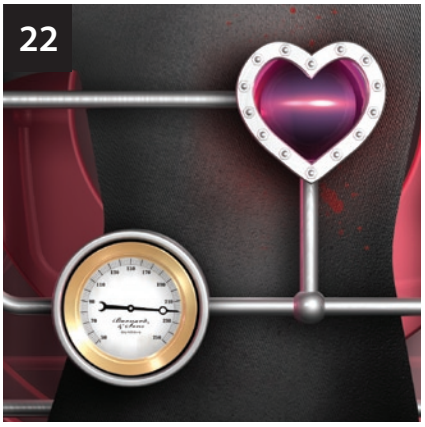

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Antimicrobial Resistance in New Zealand:

What is my role in primary care?

This month marks the launch of our 2013 revised edition of "Antibiotic choices for common infections". The guidance supports the goal of preserving the effectiveness of antimicrobial medicines. In the last edition of Best Practice Journal we looked at antimicrobial resistance from a global perspective; but what does this mean for general practice in New Zealand? The following commentary has been provided by Dr Rosemary Ikram, Clinical Microbiologist.

National surveillance of antimicrobial susceptibility

The Antibiotic Reference Laboratory at the Institute of Environmental Science and Research Ltd (ESR) is responsible for collecting national-level data on antimicrobial resistance in New Zealand. This data is obtained from routine and targeted diagnostic susceptibility testing in hospital and community laboratories, testing of isolates referred to ESR and periodic national point-prevalence surveys.

The indicators currently monitored are:

- Extended spectrum β lactamase (ESBL) in enterobacteriaceae – annual survey of isolates submitted to ESR
- Group A streptococci – included in the annual resistance data report
- *Haemophilus influenzae* – data from isolates submitted to ESR from cases of invasive disease; non-invasive disease included in the annual resistance data report
- MRSA – annual report from monthly surveys
- *Neisseria gonorrhoeae* – included in the annual resistance data report
- Salmonella – annual report which also includes comparison of travel associated vs. local isolates as well as human vs. animal isolates
- *Staphylococcus aureus* – included in the annual resistance data report
- *Streptococcus pneumoniae* – invasive isolates included in an annual report on invasive pneumococcal disease; non-invasive isolates included in the annual resistance data report
- Tuberculosis – an annual report, which includes susceptibility data
- Vancomycin-resistant enterococci (VRE) – all laboratories submit isolates for reference testing and an annual report includes susceptibility data

Annual reports on some of the above infectious diseases (MRSA, ESBL in enterobacteriacae and VRE) also contain epidemiological information, including analysis relating to each DHB region.

There is currently no official method for reporting local resistance, which is important information for prescribing in primary care. There is a significantly higher prevalence of most resistant organisms in the north of the North Island compared to the South Island. On occasions this can be reversed, e.g. in the 1990s the prevalence of penicillin resistance in community isolates of *Streptococcus pneumoniae* was higher in Canterbury than in any other region in New Zealand. Laboratories should be encouraged to produce local data on an annual basis to facilitate optimal empiric prescribing in the community.

Antimicrobial resistance in primary care

Urinary tract infection

Antibiotic treatment is indicated for all people who have symptoms of a urinary tract infection (UTI). A urine culture is not required in the case of uncomplicated infection, however, it is recommended that urine culture (and antibiotic susceptibility) is obtained for males, women who are pregnant, children and people who do not respond to empiric antibiotic treatment within two days, as well as those with "complicated" infection (i.e. other than cystitis).

The main pathogens associated with UTI are *Escherichia coli*, *Staphylococcus saprophyticus*, *Proteus spp*., *Klebsiella spp.* and *Enterococcus spp*. The current recommended antibiotic treatment for uncomplicated cystitis is trimethoprim or nitrofurantoin, with norfloxacin (a quinolone) third-line in infections resistant to the first two choices.

It is recommended that when an organism is reported to have 20% of isolates resistant to an antimicrobial, it is unsuitable as an empiric choice. This is complicated by the fact that local susceptibility data is often lacking and if it is available rates of resistance are over-reported because of the strategy of testing only urine samples from complicated cases. There are also several different species of organism which cause UTI and therefore susceptibility to antibiotic choices varies. When looking at susceptibility to determine empiric choice it is the susceptibility of *E. coli* which is usually considered. With the increasing resistance of urinary pathogens, local sentinel cultures are being requested by some laboratories, i.e. where clinicians are requested to test some uncomplicated cases so that data on local susceptibility can be produced.

The most recent ESR data from 2011 showed that trimethoprim resistance is reported at 24.4%, but nitrofurantoin resistance was encountered in just 1.1% of isolates.[1] This does suggest that trimethoprim is no longer an appropriate first-line empiric choice for UTI, however, as discussed, available resistance data may not accurately represent uncomplicated infections, and resistance varies locally.

The variation in susceptibility related to geographical area is also illustrated by the rates of ESBL-producing enterobacteriaceae around New Zealand. In the latest report (2012) there has been a 24.3% increase compared to the previous year. The majority of isolates came from the north of the North Island. A large number of these isolates are from the community, and are causing UTI.[2]

Gonorrhoea

Neisseria gonorrhoeae has become increasingly resistant to quinolones (e.g. ciprofloxacin) – resistance was reported at 41% in the 2011 data from ESR.[1] Ceftriaxone is now the treatment of choice even though the susceptibility of some strains is reduced. When treating gonorrhoea, it is important to also include azithromycin treatment for chlamydia infection as they are often concurrent. With the introduction of the new nucleic acid amplification test (NAAT) technology more cases of gonorrhoea will be identified, but currently these tests do not supply susceptibility data. Until such developments become available it will be important to obtain some cultures for susceptibility testing to guide empiric treatment of this infection. This will require discussion between clinicians and their local laboratory.

Staphylococcus aureus

Staphylococcus aureus is a frequent cause of skin infections (e.g. bites, cellulitis, impetigo, diabetic foot infections), respiratory infections (e.g. pneumonia), otitis externa and conjunctivitis.

Community methicillin resistant strains (CA-MRSA) are becoming more common; the most recent MRSA data for New Zealand (2012) show that these strains now cause the majority of MRSA infections in this country.[3] The recently reported point prevalence data shows an increase in resistant isolates of 10% between 2011 and 2012.[3] There is considerable variation of prevalence and rate of increase of MRSA between DHB regions, but MRSA is more common in the North Island of New Zealand. Overall, the ESR antimicrobial resistance report shows that 10% of *S. aureus* isolates are resistant to methicillin, i.e. MRSA,[3] but it is important to note that a larger number of isolates from the North Island will have been tested compared to the South.

Strategies to slow the emergence of community bacterial pathogens include:

- Reduce unnecessary antibiotic use

- When antibiotics are used, prescribe the correct dose and duration of treatment
- Educate patients about antibiotic use and expectations for treatment, e.g. when antibiotics are not required
- Implement infection control strategies in all health care settings, including acute hospitals and long-term care facilities

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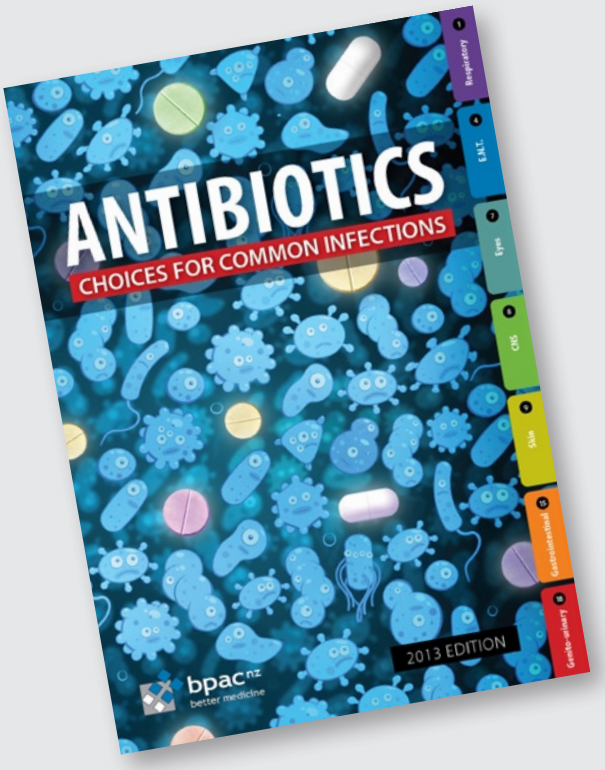
Antibiotic choices for common infections: what has changed in the 2013 edition?

In 2011, bpac[nz] produced a guide for prescribing antibiotics for common infections seen in primary care. Although published only two years ago, changing resistance patterns and new guidelines for treating infections meant that some areas needed to be updated.

This guidance was revised in consensus with adult and paediatric Infectious Diseases Physicians and a Clinical Microbiologist, to reflect current antimicrobial susceptibility patterns and best practice evidence. It is intended to aid selection of an appropriate antimicrobial, at the correct dose and duration for patients with infections commonly seen in general practice. Individual patient circumstances and local resistance patterns, however, may alter treatment choices. The guide is also available electronically on our website, and this version will be updated if required.



What are the main differences?

Pertussis

Azithromycin is now available, and subsidised (liquid and tablet forms), for the treatment and prophylaxis of pertussis. Azithromycin replaces erythromycin as the recommended first-line treatment and prophylaxis in children. The shorter duration of treatment (five days compared to 14 days with erythromycin) increases adherence. Although azithromycin is an effective option for adults for treatment and prophylaxis of pertussis, erythromycin is preferred first-line as it is important to reserve use of azithromycin, and help to slow the development of resistance.

Pneumonia

The first-line treatment for community-acquired pneumonia in adults is amoxicillin. A macrolide antibiotic should be added to the treatment regimen if atypical infection is suspected. Roxithromycin replaces erythromycin as the macrolide of choice, as it is preferred

in respiratory infections, although erythromycin would still be an effective choice. Doxycycline (added to amoxicillin) is an alternative to a macrolide for atypical infections. New guidance from Auckland DHB now recommends a higher dose of doxycycline in patients with pneumonia.

Otitis media

Antibiotic treatment is usually not required for otitis media, however, when indicated, amoxicillin remains the first-line choice. Erythromycin and cefaclor are no longer recommended as second-line choices as they are less preferred to co-trimoxazole in treating otitis media.

Sinusitis

Antibiotic treatment is usually not required for sinusitis as most patients will not have a bacterial infection, however, when indicated, amoxicillin remains the first-line choice. Co-trimoxazole and cefaclor are no longer recommended as second-line choices as they are less preferred to doxycycline in treating sinusitis.

Conjunctivitis

Framycetin is no longer a recommended treatment for conjunctivitis. It was previously a second-line option to chloramphenicol, however, it is only partly subsidised and fusidic acid is a fully subsidised, appropriate alternative second-line treatment.

Skin infections

A new section has been included in the guide on the treatment of recurrent skin infections, including staphylococcal de-colonisation. Cephalexin has been added as an appropriate treatment option for boils, cellulitis, diabetic foot infections, impetigo and mastitis. It can be used as an alternative first-line treatment in children who are unable to tolerate flucloxacillin or as a second-line option for adults. Co-trimoxazole is used to treat skin infections in the community when MRSA is present. Cefaclor is no longer favoured as a second-line alternative in these skin infections, as use must be reserved.

Travellers' diarrhoea

This section is no longer included in the guide as in most cases, antibiotic treatment is not required as the illness is viral or self-limiting. Patients with severe symptoms should be discussed with an Infectious Diseases Physician or Clinical Microbiologist to decide on an appropriate treatment regimen, depending on the causative pathogen.

Urinary tract infection

Two new sections have been included in the guide - UTI in adults and UTI in children, to replace "cystitis". UTI treatment choices remain the same for adults, however, a treatment regimen has now been included for children. Treatment is recommended for seven days in women who are pregnant and in males (previously 10 – 14 days in males).

Sexually transmitted and other genital infections

Antibiotic treatment regimens are based on the recently updated New Zealand Society for Sexual Health guidelines.

Ornidazole is an alternative to metronidazole (if metronidazole is not tolerated) in bacterial vaginosis, pelvic inflammatory disease and trichomoniasis. Ornidazole is reportedly better tolerated than metronidazole, however, it should not be used in women who are pregnant as no study data is available.

Doxycycline is an alternative first-line treatment to azithromycin for chlamydia. Erythromycin is no longer recommended as a second-line option as it is not as effective as other choices for chlamydia.

Amoxicillin clavulanate or co-trimoxazole are now the first-line choices for treating acute pyelonephritis; ciprofloxacin (previous first choice) is a second-line alternative.

The recommended ceftriaxone dose for gonorrhoea, epididymo-orchitis and pelvic inflammatory disease is now 500 mg IM, stat (previously 250 mg).

For an electronic version of the guide see:

www.bpac.org.nz/antibiotics

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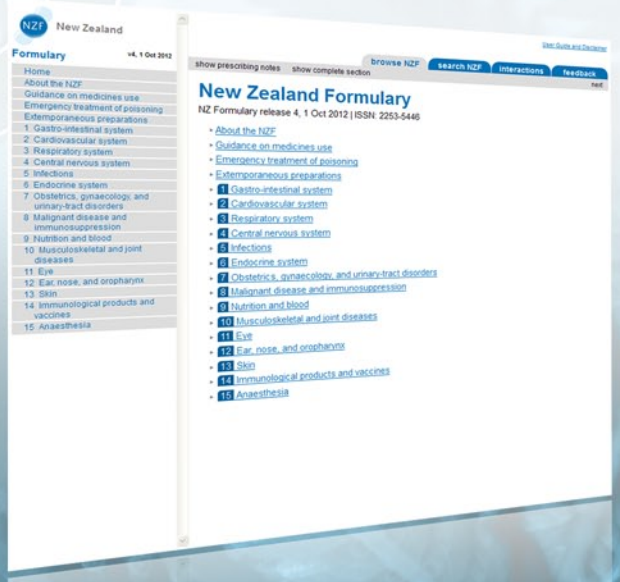

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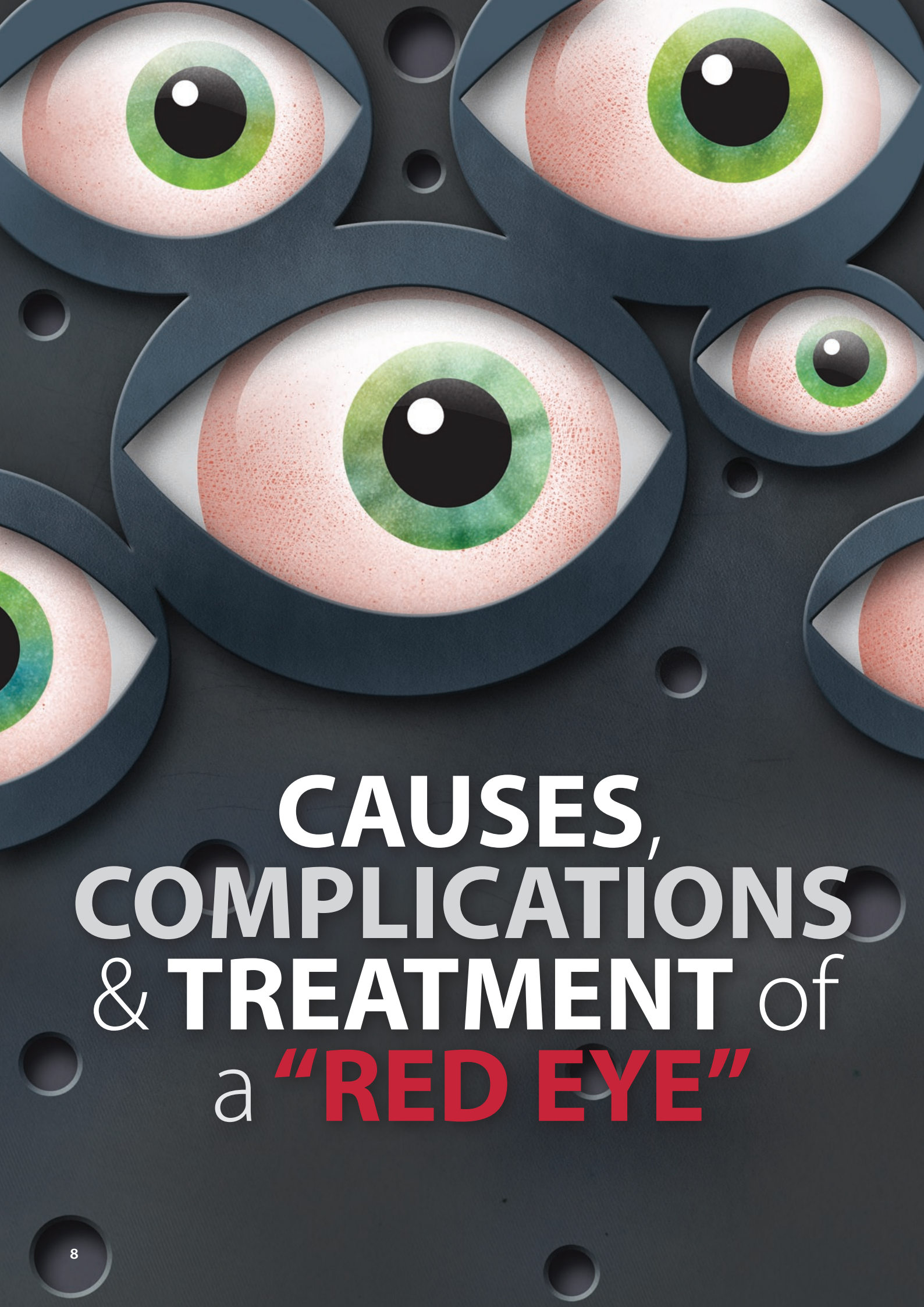


CAUSES, COMPLICATIONS & TREATMENT of a "RED EYE"

Most cases of "red eye" seen in general practice are likely to be conjunctivitis or a superficial corneal injury, however, red eye can also indicate a serious eye condition such as acute angle glaucoma, iritis, keratitis or scleritis. Features such as significant pain, photophobia, reduced visual acuity and a unilateral presentation are "red flags" that a sight-threatening condition may be present. In the absence of specialised eye examination equipment, such as a slit lamp, General Practitioners must rely on identifying these key features to know which patients require referral to an Ophthalmologist for further assessment.

Is it conjunctivitis or is it something more serious?

The most likely cause of a red eye in patients who present to general practice is conjunctivitis. However, red eye can also be a feature of a more serious eye condition, in which a delay in treatment due to a missed diagnosis can result in permanent visual loss. In addition, the inappropriate use of antibacterial topical eye preparations contributes to antimicrobial resistance.

Most general practice clinics will not have access to specialised equipment for eye examination, e.g. a slit lamp and tonometer for measuring intraocular pressure, and some conditions can only be diagnosed using these tools. Therefore primary care management relies on noting key features such as pain, photophobia and reduced visual acuity, to identify which patients require referral for ophthalmological assessment. In general, a patient with a unilateral presentation of a red eye suggests a more serious cause than a bilateral presentation.

There are six serious causes of red eye, which can result in visual loss:[1]

1. **Acute angle closure glaucoma** occurs when there is an obstruction to drainage of aqueous humour from the eye, rapidly causing increased intraocular pressure. This condition typically occurs in middle-aged to elderly, hypermetropic (long-sighted) females,[2] however, it can occur in any patient.
2. **Keratitis** is inflammation of the corneal epithelium caused by infection (e.g. herpes simplex virus, bacteria, fungi or protozoa) or auto-immune processes (e.g. collagen vascular diseases).[3] Microbial keratitis is usually precipitated by a change to normal corneal epithelial health, caused by a factor such as trauma, contact lens use or tear film and/or eyelid pathology.
3. **Iritis** is inflammation of the iris that can be associated with other inflammatory disorders, e.g. ankylosing spondylitis, or occur as an isolated idiopathic condition. Iritis is also known as anterior uveitis; posterior uveitis is inflammation of the choroid (choroiditis). Complications include glaucoma, cataract and macular oedema.
4. **Scleritis** is inflammation of the sclera. This is a very rare presentation, usually associated with autoimmune disease, e.g. rheumatoid arthritis.
5. **Penetrating eye injury or embedded foreign body**; red eye is not always a feature
6. **Acid or alkali burn to the eye**

The patient history will usually identify a penetrating eye injury or chemical burn to the eye, but further assessment may be necessary in order to determine whether a patient presenting with red eye has any "red flag" features which suggests one of these sight-threatening conditions.

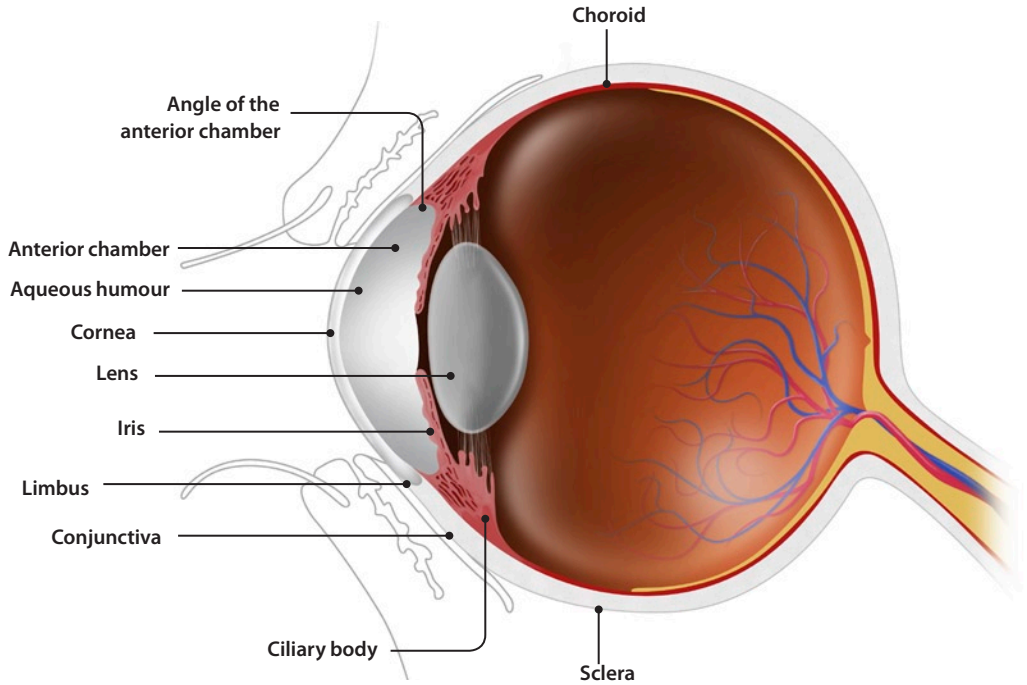
History and eye examination

The most important findings in a patient with a red eye are the presence of pain, photophobia or reduced visual acuity (Table 1, Page 13).

Ask about:

- Duration, nature and onset of symptoms
  - Dull, stabbing, throbbing or gritty pain?
  - One eye, both or sequential?
- Exposure to chemicals or other irritants, foreign body or trauma
- Photophobia
- Changes to vision; reduction in acuity, haloes, other visual disturbances
- Discharge from the eye; nature, volume and persistence
- Past ocular history
  - Previous episodes?
  - Previous herpetic eye disease?
  - Previous eye surgery?
  - Contact lens use – hygiene practices?

Anatomy of the eye



Anterior chamber The fluid filled space between the iris and the inner surface of the cornea

Angle of the anterior chamber The width of angle of the anterior chamber (iridocorneal angle) affects the drainage rate of aqueous humour from the anterior chamber into the trabecular meshwork; a narrow or closed angle reduces drainage

Aqueous humour A transparent fluid that fills the anterior chamber of the eye. Production is constant, therefore drainage is the key determinant of intraocular pressure.

Choroid A vascular layer between the sclera and retina that provides oxygen and nutrition to the retina

Ciliary body The circumferential tissue, anterior to the retina, composed of ciliary muscle and ciliary processes that change the shape of the lens to adjust focus – a process called accommodation. The ciliary processes also produce aqueous humour.

Conjunctiva A thin, clear yet vascular layer of epithelial and subepithelial tissue that covers the sclera and inside of the eyelids. Inflammation (conjunctivitis) causes vascular dilatation and can produce significant oedema of this tissue (chemosis).

Cornea The transparent, convex layer of the eye in front of the iris, pupil and anterior chamber; the cornea provides a mechanical barrier but its curvature provides most of the focusing power of the eye.

Iris A thin, opaque (coloured), circular structure that controls the size of the pupil and the amount of light that reaches the retina

Lens A biconvex structure behind the iris that helps to refract light to accurately focus on the retina

Limbus The border between the sclera and the cornea

Sclera The opaque protective outer layer of the eye (the "white of the eye") that covers everything except the cornea

- Occupational history, e.g. outdoor worker, metal fabricator, childcare worker
- The presence of any other symptoms, e.g. recent or concurrent upper respiratory tract infection, skin and mucosal lesions, muscular or skeletal pain, joint stiffness, genitourinary discharge, dysuria; these symptoms may indicate an underlying systemic cause of the red eye

Examination and assessment

The extent of the eye examination should be based on the patient's history and suspected cause of the red eye. Examination should be very brief in the case of a chemical injury to the eye as irrigation of the eye is the priority and should begin immediately. A topical anaesthetic, e.g. tetracaine, may be used if the examination is uncomfortable for the patient.[1]

Measure visual acuity of both eyes using a Snellen chart. Ensure good lighting, and use a pinhole to exclude any residual refractive error. The patient should wear their corrective distance glasses, if they have them. If the patient has discharge in their eye(s), ask them to blink several times before checking vision, to ensure that an accurate assessment is made.

Examine the eye:

- Assess the extent, location and nature of the redness of the eye(s)
  - The pattern of injection (redness) should also be noted: **conjunctival injection** (Figure 1) appears as a diffuse area of dilated blood vessels, injection in a ring-like pattern around the cornea is termed **ciliary injection** (Figure 2) and usually indicates intraocular inflammation
- Is there any discharge? Is it purulent or clear?
- Is there any evidence of hyphema (blood in the anterior chamber) or hypopyon (purulent exudate in the anterior chamber)?
- Is there swelling of the eyelids, around the eye or of the conjunctiva?
- Examine the pupils
  - Are they equal? Any irregularity of shape?
  - Measure pupillary response/light reflexes
- Examine the cornea; is it clear or opaque/hazy? Is there localised corneal opacity representing a corneal infiltrate?
  - Instill and assess the results of fluorescein dye (see below)
- Look for a foreign body or lesion on the eye, including under the eyelids; eyelid eversion may be required, but do not attempt this if the mechanism of injury and/or clinical signs suggest the possibility of a penetrating eye injury
- Examine the eyelids
  - Is lid position normal? Is lid closure complete? Any evidence of blepharitis? Are the eyelashes inturned (trichiasis)?

Assessing the cornea with fluorescein dye: Fluorescein is an orange dye that fluoresces green under blue light. It dissolves into the tear film creating a homogenous green glow across the ocular surface, with increased intensity where the tears accumulate on the lower lid margin. Any area of epithelial defect will stain brightly, allowing detection of corneal abrasions, ulcers and foreign bodies.

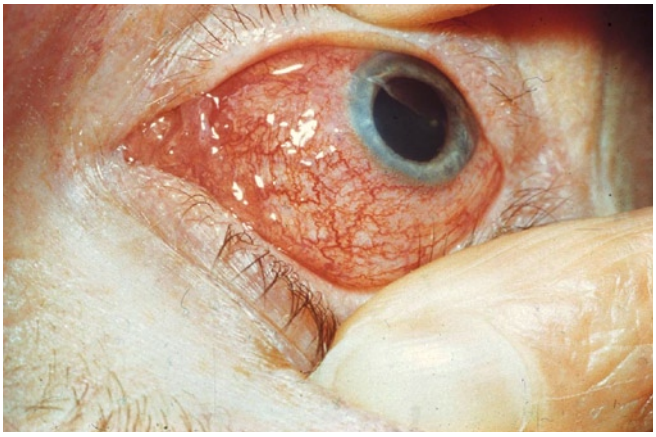


Figure 1: Conjunctival injection – showing a diffuse pattern of dilated blood vessels. Photo kindly supplied by Dr Logan Mitchell, Department of Medicine, University of Otago.

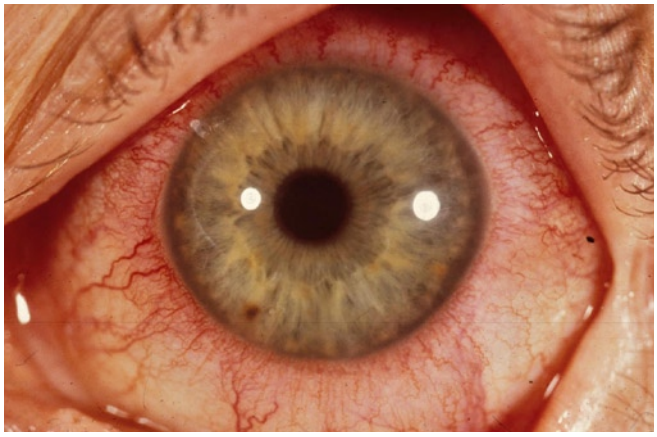


Figure 2: Ciliary injection – showing a ring-like pattern of dilated blood vessels around the cornea, which indicates inflammation of the cornea, iris or ciliary body. Photo kindly supplied by Dr Logan Mitchell, Department of Medicine, University of Otago.

Patients should be asked to remove contact lenses before fluorescein dye is applied. Instil the dye by either touching a fluorescein strip to the inside of the lower eyelid, or applying a drop of fluorescein dye eye drops; ask the patient to blink to distribute the dye. Examine the eye using a blue light (usually a direct ophthalmoscope with the cobalt blue filter) looking for areas of increased staining intensity. Note the distribution, size and pattern/shape.

Refer serious causes of red eye

"Stop!" Red flags

Patients with the following features should be referred urgently (same day) for ophthalmological assessment:[1, 4]

- Severe eye pain
- Severe photophobia
- Marked redness of one eye
- Reduced visual acuity (after correcting for refractive errors)
- Suspected penetrating eye injury
- Worsening redness and pain occurring within one to two weeks of an intraocular procedure (possible post-operative endophthalmitis, see Page 15)
- Irritant conjunctivitis caused by an acid or alkali burn or other highly irritating substance, e.g. cement powder; irrigate eye until pH neutral prior to referral (see below)
- Purulent conjunctivitis in a newborn infant (refer to a Paediatrician)

At this point in the consultation, the cause of the red eye may be obvious, e.g. foreign body, or the features may be severe enough to warrant urgent referral. Table 1 summarises distinguishing features to determine the cause of a red eye. Many patients with red eye may have ambiguous features and require a slit-lamp examination to be certain of a diagnosis. If there is any suspicion of a serious cause then discussion with an Ophthalmologist is recommended. A triage assessment by an Optometrist may also be useful, especially in remote locations.

Refer urgently for an ophthalmological assessment if the patient is suspected to have acute angle closure glaucoma, iritis, scleritis, infectious/inflammatory keratitis or a penetrating eye injury.

Patients with a serious chemical eye injury also require urgent referral but the first priority is irrigation of the ocular surface: topical anaesthetic should be applied, the eyelids held open and ≥ 500 mL of normal saline or sterile water flushed across the globe, ideally using an intravenous giving set. Check the pH of the tear film using litmus paper two to three minutes after each bag of fluid and repeat until the pH measures 7 – 8 and appears equal between the two eyes.

Patients with an injury which has penetrated the eye should be referred immediately for an ophthalmological assessment. Tetanus status should be determined, a hard shield taped over the eye (without exerting pressure on the globe), and the patient instructed not to eat or drink in preparation for possible surgery. A penetrating injury may be obvious in the case of a grossly misshapen globe or a full-thickness corneal or scleral laceration with prolapse of intraocular contents. However, subtle clues to look for include a shallowing of the anterior chamber in that eye, or tear-drop distortion of the pupil due to the iris prolapsing through an unnoticed wound, although these features may be difficult to detect without the use of a slit lamp. Patients with an injury caused by a high-velocity object, e.g. when striking metal on metal, or a sharp object, e.g. glass, thorn, knife, should be treated as having a high suspicion of penetrating injury, even if no foreign object is visible.[5]

Management of acute angle closure glaucoma

This is a medical emergency and the patient should be discussed with an Ophthalmologist immediately to determine initial management and arrange urgent assessment.

Symptoms of raised intraocular pressure are deep eye pain (described as throbbing, drilling pain), redness, blurred vision (often with haloes around lights due to corneal oedema), headache, nausea and vomiting. Suggestive signs are ciliary injection, fixed mid-dilated pupil, a generally hazy cornea and decreased visual acuity (Figure 3).

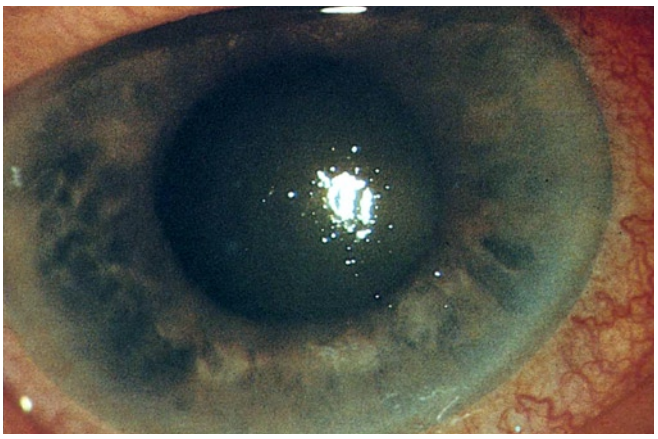


Figure 3: Acute glaucoma – showing hazy cornea, indistinct iris and fixed, mid-dilated pupil. Photo kindly supplied by Dr Logan Mitchell, Department of Medicine, University of Otago.

Table 1: Features of conditions causing red eye[1, 8, 9]

	Cause of red eye					
Feature	**Conjunctivitis**	**Subconjunctival haemorrhage**	**Keratitis**	**Iritis (anterior uveitis)**	**Acute angle closure glaucoma**	**Scleritis**
Conjunctival injection	Diffuse, unilateral or bilateral	Unilateral, not truly injected but rather discrete confluent haemorrhagic change (generalised in severe cases)	Ciliary pattern,* unilateral	Ciliary pattern, unilateral	Ciliary pattern, unilateral	Localised, unilateral
Cornea	Clear	Clear	Hazy, localised opacity (infiltrate), epithelial defect (fluorescein positive)	May be hazy	Hazy, iris detail indistinct	Clear
Pupil	Unaffected	Unaffected	Unaffected (unless secondary uveitis present)	Constricted, poor light response, may be distorted	Fixed, mid-dilated	Unaffected (unless secondary uveitis present)
Vision	Generally unaffected	Unaffected	Moderately to severely reduced	Mildly to moderately reduced.	Severely reduced, blurred, possible coloured halos around lights	May be reduced
Discharge	Yes; purulent more likely with bacterial, watery more likely with viral	Minimal (watery)	Yes; usually watery	Minimal (watery)	Minimal (watery)	Minimal (watery)
Ocular pain	Yes; gritty or stabbing pain	Generally none	Yes; usually severe	Yes; moderate to severe	Yes; usually severe (with vomiting and headache), globe tender and hard if palpated	Moderate to severe (described as deep pain), localised significant tenderness
Photophobia	No	No	Yes	Yes	Sometimes	Sometimes

* Redness in a ring-like pattern around the cornea; indicating inflammation of the cornea, iris or ciliary body

Although most General Practitioners will not have access to a tonometer (to measure the intraocular pressure), digitally palpating the globe behind closed eyelids and comparing globe firmness provides useful information. In some circumstances and locations an urgent intraocular pressure measurement by a local Optometrist may be indicated. While waiting, the patient should lie flat with their face up, without a pillow. This may decrease the intraocular pressure by allowing the lens and iris to "sink" posteriorly, opening up the drainage angle. The Ophthalmologist may recommend an immediate dose of acetazolamide 500 mg, orally or IV, before a patient travels from a remote location.

Management of keratitis, iritis and scleritis

Keratitis can result from several aetiologies, including bacterial keratitis (most commonly secondary to contact lens use) or herpetic keratitis (see "Herpes simplex keratitis"). Key features are pain, photophobia and decreased vision. In severe cases, a level of purulent exudate within the anterior chamber may be seen (a hypopyon). Refer to an Ophthalmologist for treatment, which usually involves intensive topical antimicrobials.[1]

Iritis (anterior uveitis) is often very painful due to ciliary muscle spasm. Key features also include photophobia and decreased vision, and the pupil will usually appear constricted with a poor light response and will sometimes be distorted due to adhesions. Ophthalmological assessment will confirm the diagnosis and exclude any possible infectious cause. Treatment (of non-infectious uveitis) involves topical, peri-ocular or systemic corticosteroids, as well as cycloplegics (dilating drops) to reduce pain and prevent adhesions in the eye.

Scleritis (Figure 5) is characterised by severe, intense eye pain, described as deep, drilling pain, like a toothache.[1] It is

Herpes simplex keratitis (dendritic ulcer)

Reactivation of the herpes simplex type 1 virus ("cold sores") can, in some people, result in ocular symptoms; the patient may not always be aware of a previous herpetic infection.

Active herpes simplex keratitis is an inflammation of the corneal epithelium due to viral replication and infection causing characteristic dendritic corneal ulcers. Ulcers can be seen with fluorescein dye and appear as fine, branching (i.e. dendritic) lesions (Figure 4).[6] Without the use of a slit lamp, these lesions can easily be confused with an abrasion (and vice versa).

Subsequent complications can include an inflammatory response (without active viral replication) inside the middle layer of the cornea (stromal keratitis), or inside the eye (iritis/uveitis). There is usually no corneal epithelial defect, therefore fluorescein staining is not seen in these conditions, although the cornea is usually hazy in stromal keratitis.[6]

Patients with suspected herpes simplex keratitis should be referred for ophthalmological assessment (or consider Optometrist triage if uncertain and the use of a slit lamp would assist in diagnosis). Ocular anti-viral treatment is usually given (aciclovir 3% eye ointment).[6] Recurrences (almost always in the same eye) are common and can occur many years after the previous episode. Long-term complications can include corneal scarring and visual loss.[6]

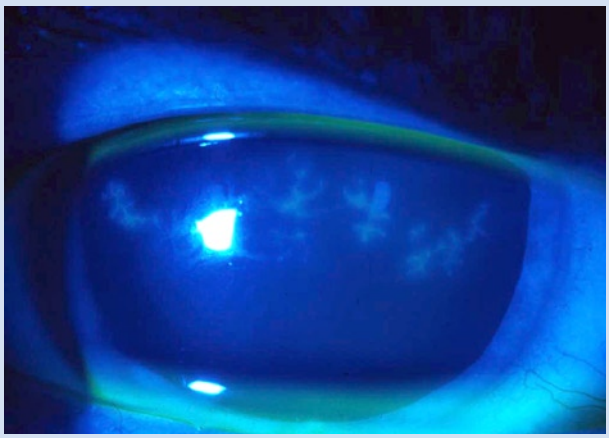


Figure 4: Dendritic ulcers – using a cobalt light and fluorescein dye, fine branching lesions (dendritic ulcers) can be seen; these are characteristic of herpes simplex keratitis. Photo kindly supplied by Dr Logan Mitchell, Department of Medicine, University of Otago.

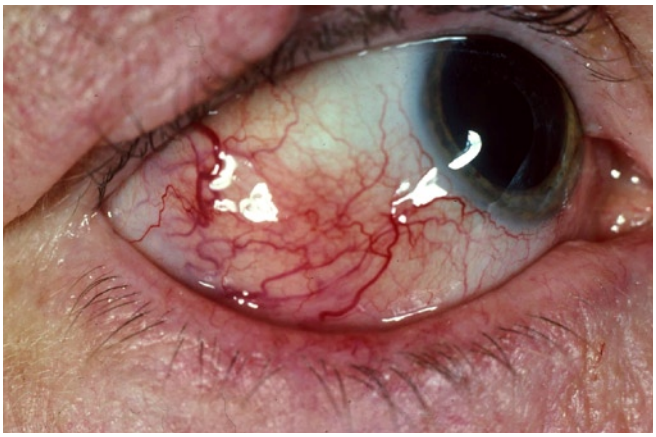


Figure 5: Scleritis – showing localised conjunctival injection. Photo kindly supplied by Dr Logan Mitchell, Department of Medicine, University of Otago.

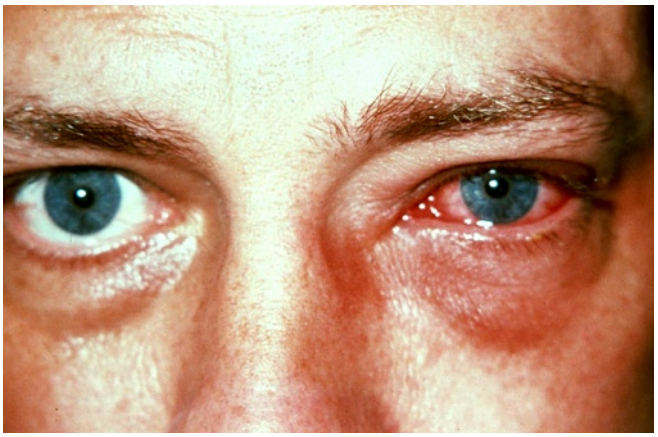


Figure 6: Viral conjunctivitis – showing diffuse conjunctival injection, watery discharge and inflammation; typically presents sequentially in one eye, then the other eyes. Photo kindly supplied by Dr Logan Mitchell, Department of Medicine, University of Otago.

usually associated with an underlying systemic autoimmune or inflammatory condition, therefore treatment focuses on the systemic cause, after Ophthalmological assessment.

For information on episcleritis, see Page 19.

Endophthalmitis

Endophthalmitis is a sight- and globe-threatening internal infection of the eye. It is most commonly iatrogenic, occurring after recent intraocular surgery (usually less than one to two weeks prior), but can rarely occur from endogenous causes such as septicaemia or endocarditis. A patient may present with worsening pain, redness and/or visual loss. A level of purulent exudate within the anterior chamber (a hypopyon) may be visible. Urgent ophthalmological assessment is required, with treatment involving sampling of intraocular fluids, intravitreal antibiotics and possibly vitrectomy surgery.

Managing red eye in primary care

Conjunctivitis

Conjunctivitis can be viral, bacterial or allergic. Bacterial and especially viral conjunctivitis are often highly contagious. As a general rule, purulent discharge indicates bacterial conjunctivitis and a clear or mucous discharge indicates viral or allergic conjunctivitis. The presence of pruritis, a history of atopy and exposure to a known allergen usually helps to differentiate allergic conjunctivitis from viral.

Viral conjunctivitis is usually caused by an adenovirus. Typical features are sequential bilateral red eyes, watery discharge and inflammation around the eye and eyelids, which can produce dramatic conjunctival swelling (chemosis) and lid oedema, to the extent that the eye is swollen shut. The patient usually reports a feeling of grittiness or stabbing pain, and may also have rhinorrhoea or other respiratory symptoms.[10] Crusting of the lashes overnight can sometimes be confused for a purulent discharge. Enlarged, tender preauricular lymph nodes are often present, and are a useful feature to assist diagnosis.[11]

As there is no effective viricidal treatment against adenovirus, viral conjunctivitis is treated supportively. Advise the patient to clean away secretions from eyelids and lashes with cotton wool soaked in water, wash their hands regularly, especially after touching eye secretions, avoid sharing pillows and towels and avoid using contact lenses. Artificial tear eye drops can be used if necessary to reduce discomfort.[11, 12]

Symptoms may take up to three weeks to resolve. In severe cases, punctate epithelial keratitis may develop – this can be seen with fluorescein staining as multiple small erosions of the conjunctiva. Patients with this complication may report ongoing discomfort for several weeks, which then resolves spontaneously.[11] Immune sub-epithelial infiltrates may develop after the conjunctivitis has settled, impairing visual acuity. These cannot be seen with fluorescein dye, and can take several weeks to resolve spontaneously.

Bacterial conjunctivitis is usually caused by *Streptococcus pneumoniae*, *Haemophilis influenzae*, *Staphylococcus aureus* or *Moraxella catarrhalis*. Less commonly, *Chlamydia trachomatis* or *Neisseria gonorrhoeae* may be the causative organism. Symptoms are similar to viral conjunctivitis, but discharge is usually mucopurulent and may cause the eyelids to become "glued" together after sleeping.[11] Symptoms are usually more

Artificial tears and lubricants

The discomfort of dry or irritated eyes may be relieved by the use of tear replacement preparations (artificial tears) and ocular lubricants. Lubricants are generally thicker, ointment-based products, which can cause blurred vision, therefore are most appropriate for use overnight. Lubricants generally should not be used while wearing contact lenses.

Artificial tear preparations traditionally contain hypromellose, carmellose, carbomers, polyvinyl alcohol, povidone (an antiseptic) or sodium hyaluronate. Sodium chloride solution is often used by people who wear contact lenses, to relieve discomfort. Paraffin is a common ocular lubricant.

The range of lubricating eye preparations (with a preservative) that are fully subsidised without restrictions has widened to include thick and thin artificial tear drops, a gel and an eye ointment. Some products are also available for purchase over-the-counter. Check the New Zealand Formulary or Pharmaceutical Schedule for subsidy information before prescribing.

Preservative-free eye preparations now subsidised

Eye treatments prepared in multi-use bottles or tubes contain a preservative to prevent contamination. This preservative is often mildly toxic to the corneal epithelium, leading to a toxic keratopathy (non-inflammatory disease of the cornea) in patients sensitive to these agents, or those receiving these drops frequently and long-term. PHARMAC has approved the funding of three preservative-free lubricating eye preparations, subject to Special Authority criteria. The Special Authority requirements are that patients must have a confirmed diagnosis, with slit lamp, of severe secretory dry eye, and either require eye drops more than four times daily on a regular basis or have a confirmed allergic reaction to preservative in eye drops. Therefore preservative-free eye preparations are likely to be initiated by an Ophthalmologist and continued in general practice.

The preparations available with Special Authority are:

- Sodium hyaluronate eye-drops 1 mg/mL (Hylo-Fresh), a preservative-free thin lubricating eye-drop; available from 1 July, 2013. N.B. In contrast to most eye preparations which have a one month expiry after opening, Hylo-Fresh has a six month expiry after opening.
- Macrogol 400 0.4% with propylene glycol 0.3% eye drops (Systane Unit Dose), a preservative-free thick lubricating eye-drop; available from 1 August, 2013
- Carbomer ophthalmic gel 0.3% (Poly-gel), a preservative-free lubricating gel; available from 1 August, 2013

Retinol palmitate 138 micrograms/g ophthalmic ointment (VitA-POS) is available from 1 July, 2013, fully subsidised (without restrictions). This is a preservative-free lubricating eye ointment for dry eyes.

For full details visit: **www.pharmac.health.nz** or **www.nzf.org.nz**

severe and persistent in patients with conjunctivitis caused by *Chlamydia trachomatis* or *Neisseria gonorrhoeae* (termed hyperacute conjunctivitis).

Bacterial conjunctivitis is self-limiting in most people and symptoms resolve without treatment within one to two weeks (although resolution may be more rapid in some people).[11, 13] Advise supportive treatment (as for viral conjunctivitis). Avoid the use of cosmetics applied to the eye area as these may be contaminated.

There has been much debate as to whether the use of topical antibiotics improves recovery time in people with bacterial conjunctivitis. A 2012 Cochrane review of 11 randomised controlled trials concluded that the use of antibiotic eye drops for bacterial conjunctivitis modestly improved the rate of "clinical and microbiological remission" and was associated with a low risk of serious adverse effects.[13] The meta-analysis found that after five days, symptoms had resolved in 30% of patients receiving placebo and in 40% of those receiving a topical broad-spectrum antibiotic. By day ten there was 41% remission in the placebo group and 50% remission in the antibiotic group.[13]

Most patients (or parents of young patients) who present to general practice with bacterial conjunctivitis will expect to receive topical antibiotic treatment. The limitations of treatment should be explained and, if appropriate, offer a "back pocket prescription" and instruct the patient (or parent) to delay starting treatment for a few days to see if the symptoms resolve.[11] Antibiotics may be started immediately if symptoms are severe or distressing. The recommended treatment for adults and children aged over two years is chloramphenicol 0.5% eye drops, one to two drops, every two hours for the first 24 hours, then every four hours, until 48 hours after symptoms have resolved. Chloramphenicol 1% eye ointment can also be used at night in patients with severe infections or as an alternative to eye drops for those who prefer this formulation. Fusidic acid 1% eye gel is an alternative to chloramphenicol, and is preferred in women who are pregnant; one drop, twice daily, until 48 hours after symptoms have resolved.

Pharmacists who have trained in the diagnosis and management of conjunctivitis may sell chloramphenicol eye preparations, subject to conditions; appropriate verbal and written information on the self-management of eye conditions must be given to all people purchasing these medicines.

Laboratory investigations (i.e. a swab) to identify bacteria and sensitivity to antibiotics are not usually required, but may be considered in immunocompromised patients or if symptoms

Herpes zoster ophthalmicus (Shingles)

Herpes zoster ophthalmicus is essentially shingles (reactivation of the varicella-zoster virus) in the ophthalmic branch of the trigeminal nerve (V).[7] All parts of the eye innervated by this nerve can be affected, causing conjunctivitis, keratitis and/or iritis, along with a periorbital vesicular rash, identical to a shingles rash seen elsewhere on the body. Although a shingles rash that involves the tip of the nose (Hutchinson's sign) is said to predict the development of herpes zoster ophthalmicus, one-third of patients without the sign have ocular complications.[7] Involvement of other cranial nerves such as II (optic neuritis), III, IV and VI (diplopia) may suggest central nervous system involvement and patients require neurological as well as ophthalmological assessment. Conjunctivitis and mild to moderate non-specific keratitis are common acute presentations, with sight-threatening corneal stromal or intraocular inflammation more likely to occur one to two weeks after the onset of vesicular rash.

Patients with suspected herpes zoster ophthalmicus should be started on oral acyclovir if they have presented within 72 hours of the onset of vesicular rash.[7] Patients with decreased visual acuity and/or corneal epithelial defect on fluorescein examination should be referred for same-day ophthalmological assessment.

Dry-eye syndrome

Keratoconjunctivitis sicca, known as dry-eye syndrome, occurs when there is deficiency or dysfunction of the tear film that normally keeps the eyes moist and lubricated.[18] It is more common in females and incidence increases with age.[18] Decreased tear production is most often age-related, but can also be due to systemic auto-immune diseases (e.g. Sjogren's syndrome) or some medicines. Tear film dysfunction is often caused by blepharitis, altered lid position (e.g. ectropion), decreased blink rate (e.g. intense concentration, Parkinson's disease), incomplete lid closure, or environmental factors.[18]

Symptoms include a feeling of dryness, grittiness or mild pain in both eyes, which worsens throughout the day. Eyes water, especially when exposed to the wind.[18] Patients are often aware that blinking or rubbing the eyes relieves symptoms. Conjunctival injection is usually mild, and fluorescein staining typically shows punctate epithelial erosions, which occur due to desiccation on the lower part of the cornea where lid coverage is least. The erosions are very small and may not be seen without magnification.

Treatment includes eyelid hygiene (see: "Blepharitis", Page 20), the use of artificial tears and managing exacerbating factors, e.g. limiting use of contact lenses, avoiding smoking, taking frequent breaks when concentrating on a screen.[18] In some cases, punctal plugs are inserted into the lower or upper tear drainage canals of the eye, to reduce dryness.

Complications of dry-eye syndrome include conjunctivitis and keratitis.

are persistent despite chloramphenicol treatment.[11] If gonococcal conjunctivitis is suspected in an adult, collect an eye swab* (before applying any topical treatment) and test for gonorrhoea and chlamydia.[14]

Newborn infants: If conjunctivitis is present in a newborn infant (aged ≤ 28 days), consider *Chlamydia trachomatis* or *Neisseria gonorrhoeae* as the cause, usually transmitted vaginally during birth. Refer the infant urgently to a Paediatrician; do not apply topical treatment. If the diagnosis is confirmed, parents will also require testing and possible treatment. Gonorrhoea can result in a sight-threatening eye infection and chlamydia can be associated with the development of pneumonia in young infants.[11] N.B. Infants who present with a "sticky eye", without conjunctival inflammation, are most likely to have poor drainage of the lacrimal duct rather than conjunctivitis, and this does not require urgent assessment.[11]

Allergic conjunctivitis is caused by a local response to an allergen, e.g. pollen, preservatives in eye drops or contact lens solution. Patients typically present with swollen, itching eye(s), irritation, mild photophobia and watery or serous discharge.[1] Symptoms are episodic in the case of seasonal allergies. Eversion of the lids often reveals a "cobble-stone" appearance of the tarsal (eyelid) conjunctiva because of the development of large papillae or swellings of the subepithelial stroma (connective tissue).

Treatment is supportive; avoid the allergen where possible, avoid rubbing the eyes, apply a cool or warm compress to relieve symptoms, use artificial tear eye drops if required. If symptoms are severe or other treatments are ineffective, prescribe antihistamine eye drops, e.g. levocabastine, or a mast cell stabiliser (takes several weeks for full effect), e.g. lodoxamide or cromoglicate sodium. Olopatadine eye drops combine antihistamine and mast cell stabilisation activity and are often effective. An oral antihistamine may also be prescribed, depending on patient preference and previous response to treatment.[1]

Patients with severe allergic conjunctivitis should have their visual acuity checked and a fluorescein examination, and then be referred to an Ophthalmologist for further assessment and possible initiation of topical corticosteroids. Vernal and atopic keratoconjunctivitis are two severe forms of allergic eye disease affecting children and young adults respectively, and can be associated with large epithelial defects on the cornea

* This is normally the same type of swab as used for genital testing for chlamydia and gonorrhoea – check with your local laboratory

(shield ulcers) that can lead to scarring, and also microbial keratitis – especially if topical immunosuppressants are being used.

Foreign bodies and corneal abrasions

Patients with a foreign body in their eye or a corneal abrasion typically present with discomfort, watery discharge, pain associated with movement of the eye, blurring of vision and photophobia.[5]

The patient may be aware of the foreign body which has entered the eye or it may have occurred unnoticed during an activity such as chiselling, hammering, grinding metal or mowing the lawn. Corneal abrasion can occur due to an accidental scratch, e.g. with a fingernail or while removing or inserting contact lenses, or by rubbing the eye, e.g. in the presence of a foreign body.

Any patient with a penetrating eye injury (or suspected) should be referred immediately for ophthalmological assessment. If ocular penetration is not suspected, examine the eye to locate the foreign body, which may be on the conjunctiva or under the eyelid. N.B. Do not attempt to evert the eyelid if there is a possibility of a penetrating eye injury as the contents of the eye may prolapse.[5]

Fluorescein dye can be used to help to detect the object or an abrasion. Although patients with a penetrating injury should be referred for treatment, if the injury is missed, and the eye is stained, a penetrating injury will be seen as a dark stream (i.e. dye diluted by aqueous) in a pool of bright green (i.e. concentrated dye); this is known as the Siedel sign, although it may be difficult to see without a slit lamp.[16]

To remove a foreign object from the eye, first apply a topical anaesthetic, e.g. tetracaine. Oral pain relief with paracetamol or ibuprofen can also be given.[16] Depending on the nature and location of the foreign object, it may be able to be removed by irrigating the eye. If this is not adequate, use a sterile cotton-tipped swab. In some cases, a more precise tool, such as the bevelled edge of a sterile needle may be required.[5] This should always be held tangential (on an angle) to the surface of the globe, with the bevel facing the globe, to minimise the chance of corneal perforation. This method can be difficult without the magnification provided by a slit-lamp microscope – if unsure, arrange for the patient to be treated where a slit-lamp is available (Optometrist, hospital emergency department or Ophthalmologist).

If the object is embedded and cannot be removed, or if after the object is removed there is a large abrasion, corneal opacity, rust ring (after removing a metal object), a distorted pupil or reduced visual acuity, refer for ophthalmological assessment.[5]

To prevent a secondary infection, in a patient with a corneal abrasion (including after removal of a foreign object) prescribe chloramphenicol 0.5% eye drops, one drop, four times daily, for seven days (or ointment, depending on patient preference). Fusidic acid eye gel 1%, one drop, twice daily, for seven days is an alternative.[5]

An eye patch or dressing is not necessary.[12] Contact lenses should be avoided until the abrasion has healed and ideally, until antibiotic treatment has finished. There is usually no need for prescription of anaesthetic drops; prolonged use can lead to corneal damage.[15]

Ideally, the patient should be reassessed in 24 – 48 hours. Refer for an ophthalmological assessment (or consider Optometrist triage) if the abrasion is not resolving, or if visual acuity deteriorates or pain increases.[5]

Subconjunctival haemorrhage

Subconjunctival haemorrhage occurs when blood vessels in the space between the sclera and the conjunctiva rupture. This may be caused by blunt trauma to the eye, coughing, sneezing or straining. In some cases, it may be associated with atherosclerosis, bleeding disorders or hypertension.[12] Subconjunctival haemorrhage, while often dramatic in appearance, is usually harmless. It is not associated with any significant pain and does not affect vision – if the patient has significant pain, photophobia and reduced vision, reconsider the diagnosis and refer them for an ophthalmological assessment if uncertain.[12]

In most patients, subconjunctival haemorrhage will resolve without treatment in one to two weeks.[12] Use of artificial tears may relieve any discomfort. Check the patient's blood pressure and, if they are taking warfarin, it is recommended that their INR level is checked.[12]

Episcleritis

Episcleritis is a local inflammation of the superficial top layer of the sclera.[12] Patients present with dilated superficial blood vessels in a localised area of the sclera, as opposed to conjunctivitis which appears more diffuse. Patients usually report mild pain only, discharge and photophobia are usually absent and vision is unaffected.[12] Localised tenderness is a helpful diagnostic feature.

Episcleritis resolves without treatment, within approximately three weeks. Artificial tears may be used to relieve discomfort,[12] and an oral non-steroidal anti-inflammatory drug (NSAID) such as ibuprofen, used if required. If symptoms worsen, consider the possibility of scleritis.

Blepharitis

Blepharitis is a chronic inflammation of the margin of the eyelids, which can present in patients as a "red eye", with burning, pruritis and discharge. It is frequently seen in older people, and people with rosacea and seborrhoeic dermatitis.[17] Blepharitis is caused by dysfunctional secretions of the Meibomian glands, oil-secreting glands in the eyelid margin which help the tears to distribute evenly across the ocular surface and decrease tear evaporation. These dysfunctional secretions lead to a chronic inflammatory state within the lid, and the resultant dysfunctional tear film leads to dry eye symptoms and signs (see "Dry-eye syndrome"). When diagnosing blepharitis, consider the possibility of squamous cell, basal cell or sebaceous cell carcinoma of the eyelid margin (marked eyelid asymmetry may indicate this), dermatitis or infection (e.g. impetigo).[17]

Treatment focuses on improving the Meibomian gland secretions, but is never curative and it should be explained to patients that management needs to be ongoing. As blepharitis is a chronic condition, relapses and exacerbations can be expected.[17]

The following regimen should be initially carried out twice daily, then as symptoms improve, once daily:[17]

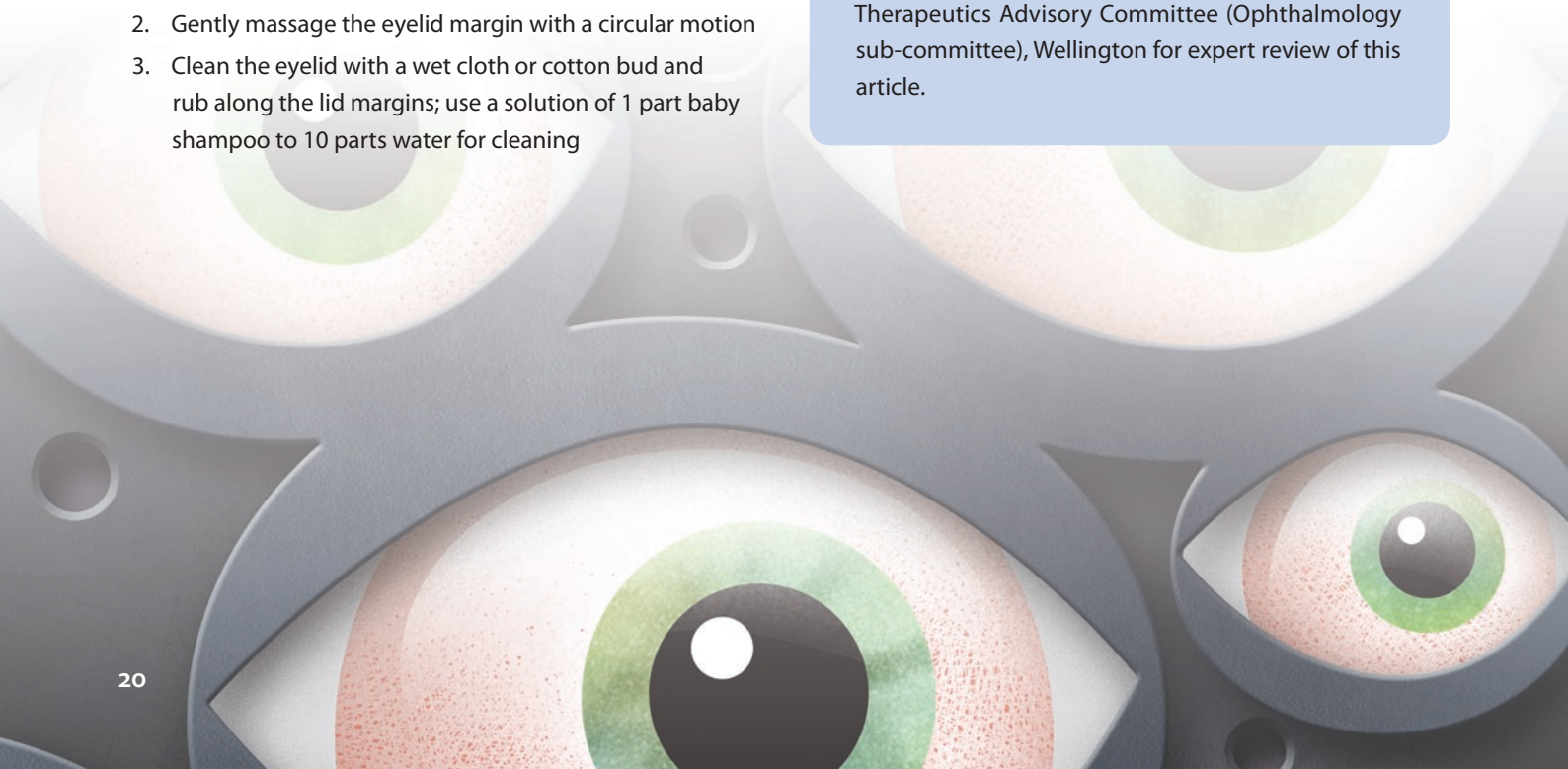
1. Apply a warm compress to the closed eyelids for five to ten minutes
2. Gently massage the eyelid margin with a circular motion
3. Clean the eyelid with a wet cloth or cotton bud and rub along the lid margins; use a solution of 1 part baby shampoo to 10 parts water for cleaning

The use of cosmetics around the eye should be avoided, especially eye liner. Artificial tears may assist in relieving symptoms.

If the symptoms are particularly severe, topical antibiotics can be considered; chloramphenicol 0.5% eye drops, one to two drops, four times daily, for seven days (or up to six weeks in chronic cases).[12, 17] Fusidic acid eye gel 1% is an alternative. In some cases, oral tetracyclines, e.g. low dose doxycycline, may be considered if topical antibiotics have not resulted in an adequate response. Antibiotics are usually prescribed initially for six weeks, but may need to be continued for up to three months, and repeated intermittently.[17] Eyelid hygiene should be maintained throughout treatment.

Blepharitis does not permanently affect vision, as long as complications are adequately managed.[17] People with blepharitis have an increased risk of developing conjunctivitis and keratitis.[17] Long-term complications include loss of eyelashes (madarosis), misdirection of lashes towards the eye (trichiasis) and depigmentation of the lashes (poliosis).[17]

ACKNOWLEDGEMENT: Thank you to **Dr Logan Mitchell**, Consultant Ophthalmologist, Dunedin Hospital, Senior Lecturer, Dunedin School of Medicine, University of Otago and **Peter Grimmer**, Optometrist, and member of the PHARMAC Pharmacology and Therapeutics Advisory Committee (Ophthalmology sub-committee), Wellington for expert review of this article.



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Hazardous Substances

Hazardous Substances Disease & Injury Notification

The Hazardous Substances & Lead Notifications reporting form is a new electronic notification system designed by BPAC Inc for general practices to report incidents related to exposures to hazardous substances.

A hazardous substance is anything that can explode, catch fire, oxidise, corrode or be toxic to humans, as defined in the *Hazardous Substances and New Organisms Act 1996*. The Act requires medical practitioners to notify cases of injury or disease caused by exposure to a hazardous substance to the Medical Officer of Health.

The form is available to health professionals at no cost, funded by the Ministry of Health.

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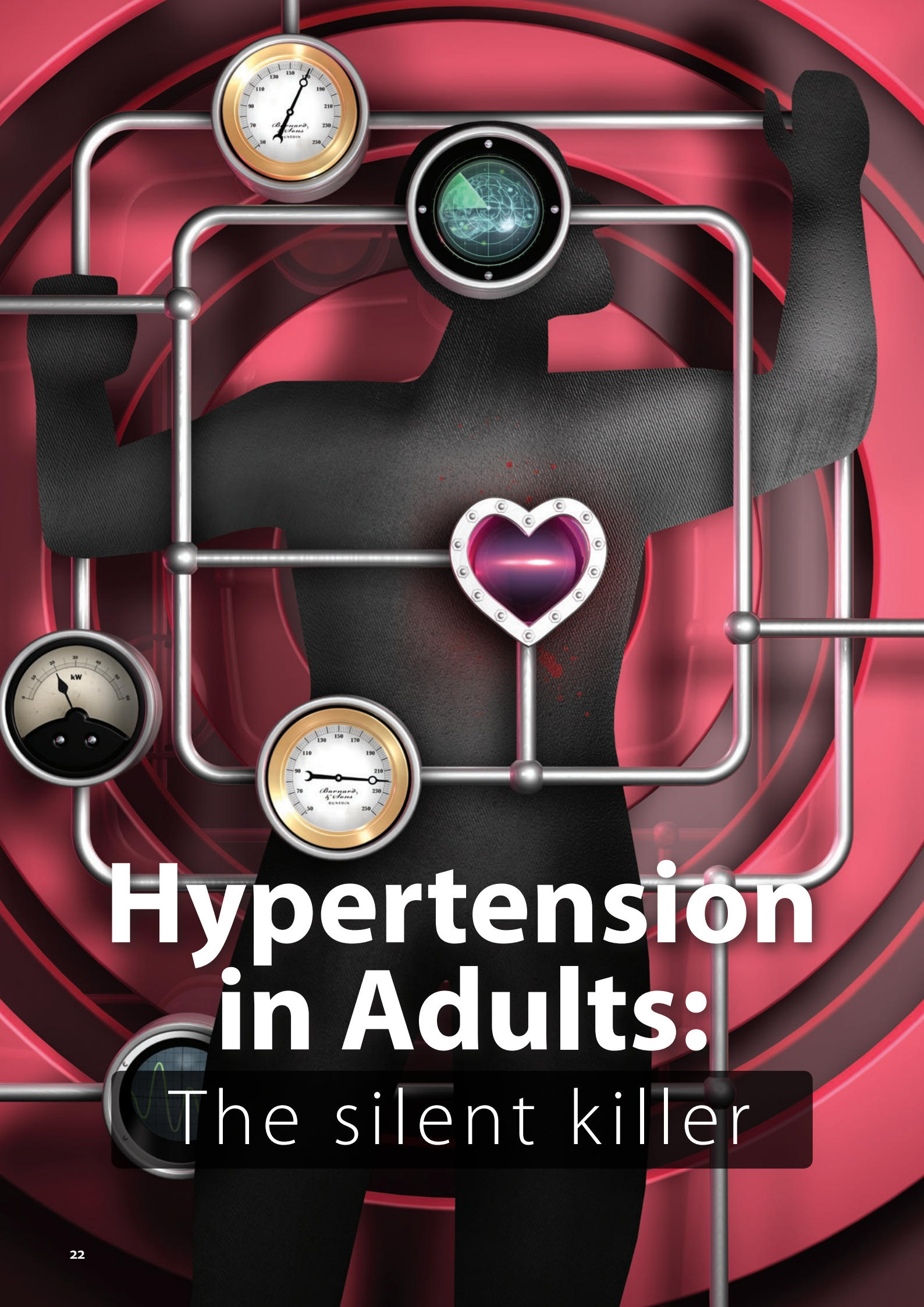


Hypertension in Adults:

The silent killer

Hypertension is associated with a wide-range of cardiovascular and end-organ diseases. It is a frequent finding among patients in primary care. However, the ideal management of hypertension continues to be debated. What is agreed is that hypertension is under-treated in New Zealand. Blood pressure is an important modifiable risk factor for cardiovascular and kidney disease and, when appropriate, clinicians should consider starting treatment in patients with hypertension, regardless of their overall cardiovascular risk. It is recommended that ambulatory or home measurement of blood pressure should ideally be offered to all patients suspected of having hypertension to confirm a diagnosis. Hypertension is progressive and management will usually require multiple medicines to achieve blood pressure targets and reduce overall cardiovascular risk

Hypertension is a continuum requiring regular review

Hypertension is a risk factor for many conditions including stroke, myocardial infarction, heart failure, atrial fibrillation, kidney disease and cognitive decline.[1] It is described as a silent killer because it is insidious, chronic and progressive.[2]

In New Zealand, the mean systolic blood pressure of many people is increasing due to the rise in obesity, sedentary lifestyles and the increasingly high fat, sugar and salt content of food.[3] It is now estimated that over one-third of adult males and over one-quarter of adult females have hypertension.[3] However, the condition is often under-treated with only 13.6% of New Zealand males and 16.3% of New Zealand females reporting use of an antihypertensive medicine.[3] The New Zealand Guidelines Group (NZGG) Primary Care Handbook (2012) states that treatment decisions for hypertension should be based solely on an individual's five-year cardiovascular risk.[4] United Kingdom NICE guidelines recommend treating hypertension in some patients independently, as a modifiable risk factor for cardiovascular and kidney disease (see "Balancing total cardiovascular risk against modifiable risk factors").[1]

Management requires individual assessment

Cardiovascular risk assessment tools may substantially underestimate the lifetime risk in younger adults when blood pressure is the only significant risk factor.[1] This is because short-term risk assessment is powerfully influenced by age.[1] The presence of end organ damage is an important factor when making treatment decisions in patients when traditional risk scores do not indicate a high overall cardiovascular risk.

The prevalence of hypertension increases steeply with age.[6] Routine surveillance of blood pressure in primary care therefore should be more frequent in older people.

Defining hypertension

Blood pressure has a normal distribution across the general population and the cardiovascular risk associated with increasing blood pressure is continuous. For every 2 mmHg increase in systolic blood pressure the risk of death from ischaemic heart disease and stroke rises by 7% and 10% respectively.[1] The line between normotension and hypertension is therefore arbitrary and patients should be encouraged to make lifestyle adjustments to control or reduce their blood pressure before they are diagnosed with hypertension.[1]

Hypertension is diagnosed and classified in the same way in all adults, however, treatment targets are individualised on the basis of age and other co-morbidities.

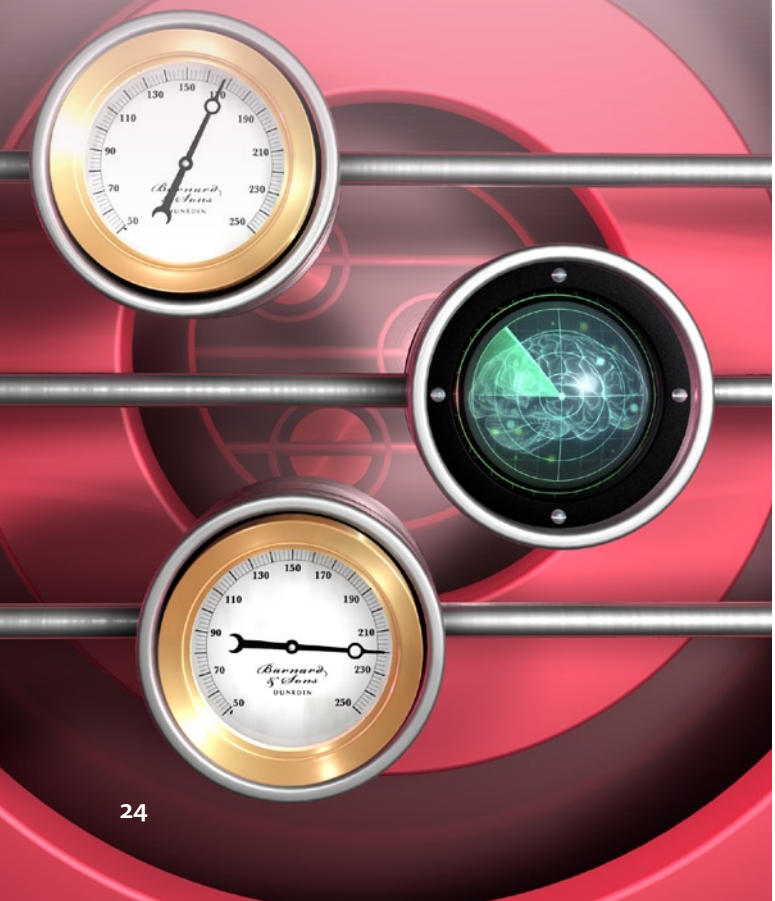
Adult hypertension
An intermediate blood pressure level is described as a blood measurement of 120-139/80-89 mmHg.

Stage one (mild) hypertension is defined as a clinic blood pressure measurement of ≥ 140/90 mmHg, or an average daytime ambulatory blood pressure measurement of ≥ 135/85 mmHg.[1]

Chronic hypertension before pregnancy is a risk factor for pre-eclampsia, therefore all women of childbearing age should have their blood pressure checked regularly and hypertension treated.[5] Blood pressure control during the first 20 weeks of pregnancy is recommended to reduce the risk of complications such as pre-eclampsia, placental abruption and impaired fetal growth.[5] A previous history of pre-eclampsia is also associated with a four-fold increased risk of a female later developing hypertension.[6]

Balancing total cardiovascular risk against modifiable risk factors

The advantage of basing treatment decisions on total cardiovascular risk is that the majority of people with hypertension have other cardiovascular risks, which are often additive and lead to a risk "that is greater than the sum of its parts".[6] In addition, hypertension in high-risk people is often resistant to treatment and requires multiple interventions, e.g. lipid modifying treatment.[3] However, the disadvantage of relying solely on five-year cardiovascular risk is that treatment may be withheld from some people because their cardiovascular risk is assessed as being too low to require treatment. For example, a 35 year old Māori male who is obese, with a total cholesterol:HDL ratio of 7.8, and a blood pressure of 165/98 mmHg has an absolute cardiovascular risk of 9% (calculated with a decision support tool) and therefore management by lifestyle interventions alone is recommended until the patient reaches the age of 46 years.[4] When considering antihypertensive treatment in younger patients with a cardiovascular risk of less than 15%, the long-term burden of disease needs to be taken into account. It is currently being debated internationally if a five year period is long enough to meaningfully convey cardiovascular risk in younger patients.



Stage two (moderate)hypertension is defined as a clinic blood pressure measurement of ≥ 160/100 mmHg, or an average daytime ambulatory blood pressure measurement of ≥ 150/95 mmHg.[1]

Severe hypertension is defined as a systolic pressure of ≥ 180 mmHg, or a diastolic pressure of ≥ 110 mmHg.[1]

Isolated systolic hypertension is defined as a clinic systolic blood pressure of ≥ 160 mmHg and diastolic < 90 mmHg.[1]

Isolated diastolic hypertension is defined as a clinic diastolic blood pressure of 90 mmHg or higher and a clinic systolic pressure of less than 140 mmHg.[7]

Diagnosing hypertension

Treatment of hypertension often involves lifelong exposure to multiple medicines and their potential adverse effects. It is therefore essential that hypertension is accurately diagnosed in primary care.

Measuring blood pressure

It is common practice in consultations to record the blood pressure of a patient, with no prior history of hypertension, from a single measurement due to time constraints. However, to achieve a more accurate assessment it is recommended that at least two blood pressure measurements be taken, at least two minutes apart.[1] Ideally, measurements should be taken from both arms. If the difference between the arms is more than 20 mmHg, the measurements should be repeated.[1] If this difference persists then subsequent measurements should be taken from the arm with the highest reading.[1] Consistent differences in blood pressure measurements of greater than 10 mmHg between arms is associated with increased cardiovascular risk.[6]

Ambulatory or home testing of blood pressure should be considered whenever substantial differences persist between clinic blood pressure measurements to exclude the possibility of "white-coat" hypertension (where the patient's blood pressure is raised due to the anxiety of having it measured in the clinic, see opposite).

If the clinic blood pressure is ≥140/90 mmHg a clinical evaluation should be conducted in order to:

1. Confirm a diagnosis of hypertension
2. Assess the patient's cardiovascular risk
3. Determine if any end organ damage has occurred
4. Detect any causes of secondary hypertension

In patients with severe hypertension (systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥110 mmHg) initiation of treatment should be considered immediately, before the diagnosis of hypertension is confirmed, e.g. with ambulatory monitoring.[1]

Confirming a diagnosis of hypertension

Ambulatory monitoring of blood pressure is the gold standard for confirming a diagnosis of hypertension and should ideally be offered to patients with a clinic blood pressure of ≥ 140/90 mmHg, where availability and cost allow.[1] A number of meta-analyses have reported that ambulatory blood pressure is a more sensitive predictor of cardiovascular risk than clinic blood pressure in patients in primary care.[6] Twenty-four hour ambulatory monitoring provides half hourly blood pressure measurements during the day and hourly measurements at night. It is an ideal method for primary care clinicians to detect white-coat or masked hypertension. Ambulatory measurement of blood pressure can also provide additional information about secondary causes of hypertension, e.g. elevated night-time blood pressure, which may suggest obstructive sleep apnoea, and increased renal and cardiovascular risk. It can therefore be a useful prognostic tool to improve the accuracy of cardiovascular risk assessments.[8]

White-coat hypertension is defined as a difference of more than 20(systolic)/10(diastolic) mmHg between clinic and daytime out-of-clinic blood pressure measurements.[1] White coat hypertension occurs in 9 – 16% of the general population, and approximately 55% of people with mild hypertension and 10% of people with severe hypertension.[6] People with white-coat hypertension are more likely to develop hypertension in the future.[6]

Masked hypertension is the opposite of white-coat hypertension and occurs when out-of-clinic blood pressure readings are higher than measurements taken in the clinic. This is also referred to as isolated ambulatory hypertension.[6] Masked hypertension affects 10 – 17% of the general population.[6] Meta-analyses of studies indicate that cardiovascular events occur approximately twice as often in people with masked hypertension as people with sustained hypertension.[6] Masked hypertension should be suspected in people with high-normal clinic blood pressure measurement, or patients with normal clinic blood pressure measurement and asymptomatic organ damage or high total cardiovascular risk.[6]

Home blood pressure measuring is an acceptable alternative to ambulatory monitoring if the patient cannot tolerate 24-hour monitoring, or if a practice does not have access to ambulatory monitoring equipment.[1] Home measurement of blood pressure gives a more accurate assessment of the likelihood of end organ damage occurring, compared to office-based measurements alone.[6] Home measurements should be taken (by the patient) in a quiet room while seated, with back and arm support.[6] Two consecutive measurements should be taken in the morning and the evening for at least four days.[1] The measurements taken on the first day are disregarded, and the average measurement calculated from the remaining results.[1]

Perform a cardiovascular risk assessment

A cardiovascular risk assessment should be undertaken for any patient with hypertension (also see "PHO Performance Programme", Page 31). Risk assessment forms the basis for discussions about prognosis and treatment options with the patient and also provides information about other factors affecting cardiovascular disease management, e.g. diabetes medicines, and primary and secondary prevention of myocardial infarction and stroke. When all risk factors are taken into account, an individual's cardiovascular risk may be higher than individual risk-factors may suggest.

Investigate for end organ damage and co-morbidities

People who are diagnosed with hypertension require assessment for end-organ damage. Investigations for end-organ damage and cardiovascular risk should include:[1]

- Dipstick urine test for haematuria and proteinuria
- Quantification of urinary protein with either an albumin:creatinine ratio (ACR), or protein:creatinine ratio (PCR)
- Blood sample to measure creatinine (eGFR), electrolytes, HbA_{1c}, lipids, urate
- Ophthalmoscopic examination of the fundus looking for features such as copper and silver wiring, AV nipping and retinal haemorrhages
- An ECG to assess for signs of left ventricular hypertrophy (consider referring for an echocardiogram if secondary causes for hypertension are suspected)

If symptoms are suggestive of obstructive sleep apnoea or treatment resistance is suspected to arise from obstructive sleep apnoea, then consider the need for a sleep study.

Consider secondary causes of hypertension

The vast majority of people with hypertension have essential (or primary) hypertension. This is by definition hypertension

"As tut lost summut?"

The potential pitfalls of relying solely on clinic-based blood pressure measurements when diagnosing hypertension, and the value that ambulatory blood pressure monitoring can provide, are illustrated in the following traditional story:

> *In 1930, Oswaldtwistle, Lancashire had only one street lamp. It was dark when George took his stroll to the Royal Oak. He sees Joe on hands and knees groping in the light of the solitary lamp. "Wot's uup lad?" George says, "As tut lost summut?" "Aye, a pound note" is the reply. "Oh, I help thee find it!" George joins Joe in the November mud. They search together. A quarter of an hour goes by, half an hour, as the hour approaches George, weary and thirsty asks plaintively: "I can't find naught! Aren't they sure thou lost it here?" "Ooh No." replies Joe, "I dropped it up street but there is no light up there!"*

This has also been referred to as parking-lot science – looking for something not where it is most likely to be, but under the streetlight, where it is most convenient. What can be seen is not always the most important thing to look at.

without an identifiable cause. Essential hypertension is thought to result from genetic predisposition and various environmental influences that are not completely understood. Risk factors that have been identified include increased weight, ageing, lack of regular exercise and dietary factors such as high salt intake (including soy sauce) and excessive liquorice consumption.[6]

Patients who are aged under 40 years with stage one (mild) hypertension and no evidence of target organ damage, cardiovascular disease, kidney disease or diabetes may benefit from further examination of possible secondary causes of hypertension and a more detailed assessment of potential end organ damage.[1] This is because short-term risk assessment (five-year predictive risk) can underestimate the lifetime risk of cardiovascular events in these people.[1]

Secondary causes of hypertension include:[4, 6, 9]

- High alcohol intake
- Obstructive sleep apnoea
- Medicines, e.g. oral contraceptives and corticosteroids, non-steroidal anti-inflammatory medicines (NSAIDs), ciclosporin and decongestants, e.g. phenylephrine
- Drug misuse, e.g. amphetamine or cocaine use
- Renal parenchymal disease, including glomerulonephritis, suggested by a history of urinary tract infection or obstruction, haematuria, analgesic misuse, or family history of polycystic kidney disease
- Renal artery stenosis
- Primary hyperaldosteronism (Conn's syndrome) suggested by significantly raised blood pressure in otherwise well people, hypokalaemia and a family history of the syndrome in some people
- Cushing's syndrome – excessive cortisol production
- Phaeochromocytoma – a rare adrenal gland tumour

Management of hypertension

Hypertension is a condition that requires lifelong treatment with regular review and usually intensification of management. There are only a limited number of people with hypertension that can be effectively managed with monotherapy.[6]

Individual blood pressure targets

Blood pressure targets should be individualised according to a patient's age and the presence of co-morbidities. A target blood pressure of < 140/90 mmHg is appropriate for most

people aged under 80 years.[1] Patients with chronic kidney disease (CKD), diabetes or cardiovascular disease should aim for a target blood pressure of < 130/80 mmHg.[4, 10] Lower blood pressure targets should be approached with caution as a systolic blood pressure of < 120 mmHg is associated with a greater frequency of serious adverse effects in people with type 2 diabetes.[4] In people aged over 80 years a target of < 150/90 mmHg is recommended.[1, 11]

If out-of-clinic monitoring of blood pressure is used, a target of < 135/85 mmHg for uncomplicated hypertension in people under age 80 years, or < 145/85 mmHg for people over age 80 years is recommended.[1]

Life-style modification is always important

The patient's diet, weight, level of exercise, alcohol consumption and smoking status should be recorded and the patient urged to make positive life changes. Blood pressure control and treatment adherence should be followed-up regularly at future consultations.

Excessive salt intake plays a significant role in hypertension as well as contributing to resistant hypertension.[6] Daily salt intake for most people ranges from 9 – 12 g per day.[6] People with hypertension who are able to reduce their salt intake to approximately 5 g per day can achieve a reduction in systolic blood pressure of 4 – 5 mmHg.[6] The benefits of salt reduction are greatest for people at increased cardiovascular risk, e.g. older people and people with diabetes or CKD.[6] Decreasing the amount of processed food in the diet is the best way to achieve this as approximately 80% of dietary salt is "hidden" in processed food.[6]

The New Zealand Heart Foundation has resources available to promote healthy lifestyles, e.g. "A guide to heart healthy eating" and "The Pacific heartbeat programme". The Heart Foundation's "Know your numbers" tool allows patients to calculate their 5-year cardiovascular risk by answering a simple questionnaire.

When to initiate antihypertensive medicines

Antihypertensive treatment is indicated for the following patients:[1, 4]

1. Patients with blood pressure ≥ 160/100 mmHg, i.e. Stage 2 (moderate) or severe hypertension
2. Any patients with hypertension who have **any** of the following factors:
   - Evidence of target organ damage
   - Cardiovascular disease
   - Renal disease
   - Diabetes
   - Five-year cardiovascular risk ≥ 15%

Patients aged under 40 years with a cardiovascular risk < 15% with stage one hypertension (140 – 160/90 – 100 mmHg), who do not have any other criteria for the treatment of hypertension, may still require management of blood pressure.[1] Consider referring these patients for more extensive evaluation for end organ damage, e.g. echocardiogram, and specialist assessment for secondary causes of hypertension.[1]

Patients with isolated systolic hypertension, e.g. > 160 mmHg, should be offered the same treatment as people with elevated systolic and diastolic blood pressure.[1]

Patients with isolated diastolic hypertension without significant co-morbidities should be treated according to their overall cardiovascular risk. The importance of isolated diastolic hypertension is considered to be less than isolated systolic hypertension.[7]

Patients with an intermediate blood pressure level, i.e. between 120 – 139/80 – 89 mmHg, should be encouraged to implement lifestyle measures to control or reduce their blood pressure and prevent being diagnosed with hypertension.

Intensification of treatment

The main benefits of antihypertensive treatment are due to the blood pressure lowering properties of medicines.[6] Furthermore, most people who are being treated for hypertension will require multiple medicines and increased doses to achieve treatment targets. Therefore the decision of when to initiate treatment is more important than which medicine is chosen. Choice of medicine is also influenced by the presence of co-morbidities and other clinical findings (see Table 1).

Adding combination treatment early often results in a greater number of patients responding more quickly to treatment compared to those on monotherapy.[6] There are also synergies in pharmacology when antihypertensive medicines are combined, which may assist in reducing blood pressure further and result in less adverse effects.[6] In patients who are at high-risk of a cardiovascular event, especially those with significant proteinuria, combination treatment is likely to be required with the use of three to four different medicines. Patients at high risk should be reviewed on a two-weekly basis to adjust doses and introduce other medicines to reduce blood pressure to target and potentially reverse proteinuria.

Table 1: Treatment guidance for primary prevention in patients with hypertension[1,6]

Step one treatment for primary prevention in patients with uncomplicated hypertension is an ACE inhibitor or calcium channel blocker: **Step two treatment**, combine an ACE inhibitor or ARB with a calcium channel blocker. **Step three treatment**, add a thiazide diuretic e.g. indapamide. N.B. Females of reproductive age should generally not be prescribed an ACE or ARB. Beta-blockers, e.g. metoprolol, or calcium channel blockers, e.g. felopidine, are recommended.
If the patient has diabetes or there is evidence of end organ damage, e.g. left ventricular hypertrophy, proteinuria, an ACE inhibitor should be prescribed first-line. **Consider a beta-blocker in combination** early when: ■ **Ischaemic heart disease** or **heart failure** is present – to reduce mortality ■ **Atrial fibrillation** is present – for rate control **If peripheral vascular disease is present** an ACE inhibitor should be considered to slow disease progression, or a calcium channel blocker to vasodilate the peripheral arteries

Step one treatment

In younger patients (NICE guidelines suggest those aged under 55 years) with hypertension, an ACE inhibitor or, if not tolerated, an angiotensin II receptor blocker (ARB) is the first treatment step.[1] ACE inhibitors or ARBs are generally effective and very well tolerated and should be the first choice for most patients with hypertension. ACE inhibitors and ARBs should not be prescribed concurrently without the recommendation of a Diabetologist or Nephrologist.[4] Females of child bearing age should also not be treated with ACE inhibitors or ARBs due to the risk of foetal abnormalities.[6] Table 2 provides guidance on doses for antihypertensive medicines.

In older patients (NICE guidelines suggest those aged over 55 years) with hypertension, initial treatment with a calcium channel blocker may provide greater benefit than an ACE inhibitor.[1] However, ACE inhibitors have also been shown to provide substantial benefits to older patients with hypertension in certain clinical situations (Table 1).[11]

Step two treatment

Step two treatment involves either the addition of a calcium channel blocker for younger patients, or an ACE inhibitor or ARB for older patients (Table 1).[1]

This guidance reflects the fact that most people with hypertension will require multiple medicines and that the combination of a calcium channel blocker with an ACE inhibitor is considered to be the most beneficial. The ACCOMPLISH (Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension) trial found a significant benefit in the combination treatment of a calcium channel blocker (amlodipine) plus an ACE inhibitor (benazepril), compared to the combination of benazepril plus a thiazide diuretic (hydrochlorothiazide).[1]

Step three treatment

Add a thiazide diuretic; indapamide and chlortalidone (chlorthalidone) have the strongest evidence of effectiveness in the treatment of hypertension and are preferred to conventional thiazides, such as bendroflumethiazide (bendrofluazide) or hydrochlorothiazide.[1] However, patients who are already being successfully treated with bendroflumethiazide do not need to be switched unless more intensive treatment is required.[1] The addition of a thiazide diuretic may help to reduce peripheral oedema associated with the use of calcium channel blockers. Patients taking diuretics should have their serum electrolytes monitored as hypokalaemia and hyponatraemia are known adverse effects.[12] Thiazide diuretics should also be prescribed with caution in younger patients as they can potentially increase the incidence of new-onset diabetes, particularly in high doses or when combined with a beta-blocker.[13]

Table 2: Recommended doses for commonly used antihypertensive medicines in New Zealand[12]

Class	Fully-subsidised option	Usual adult dose range
ACE inhibitors	■ Cilazapril	500 micrograms – 1 mg, once daily, adjusted according to response. Maximum 5 mg daily.
	■ Quinapril	10 mg, once daily. Maintenance dose, 20 – 40 mg, daily in divided doses.
	■ Enalapril	5 mg, once daily. Maintenance dose 20 mg, once daily, maximum 40 mg daily.
	■ Lisinopril	4 mg, once daily in the morning for one month. Adjusted according to response to a maximum of 8 mg, daily.
Angiotensin-II receptor blockers (ARBs)	■ Candesartan	8 mg, once daily, initially and as maintenance dose. Can be increased at two - four week intervals if necessary to a maximum of 32 mg, daily.
	■ Losartan	50 mg, once daily. Less if aged > 75 years. Can be increased to 100 mg, once daily, after several weeks.
Calcium channel blockers	■ Felopidine	5 mg, once daily in the morning (2.5 mg in older patients). Maintenance dose, 5 – 10 mg, once daily.
	■ Amlodipine	5 mg, once daily. Maximum dose 10 mg, once daily.
	■ Diltiazem	120 – 180 mg, modified release, once daily, increased if necessary every two weeks to a maximum of 240 - 360 mg, daily.
Diuretics	■ Chlortalidone	12.5 – 25 mg, once daily in the morning. Electrolytes and kidney function should be assessed before increasing the dose to 25 mg.
	■ Indapamide	2.5 mg, once daily in the morning
	■ Bendroflumethiazide	2.5 mg, once daily in the morning
Beta-blockers	■ Metoprolol succinate	47.5 mg, once daily. Increased if necessary. Maximum, 190 mg daily (slow release formulation).
	■ Atenolol	25 – 50 mg, once daily
	■ Celiprolol	200 mg, once daily in the morning. Maximum 400 mg daily.
	■ Bisoprolol	5 mg, once daily in the morning, increasing to a maximum of 20 mg daily.
ACE inhibitors with diuretics	■ Cilazapril + hydrochlorothiazide	5/12.5 mg, once daily
	■ Quinapril	10/12.5 mg, once daily. If necessary increased to 20/25 mg, once daily.

N.B. The doses in this table are from the New Zealand Formulary; some clinicians may recommend alternative dosing strategies, e.g. initiating treatment at lower doses before increasing to achieve target blood pressure.

Beta-blockers are no longer recommended as an initial treatment

Beta-blockers do not reduce the risk of stroke as much as other antihypertensive medicines and are generally poorly tolerated.[14] However, for people with ischaemic heart disease or heart failure they may be a good treatment choice (Table 1, previous page).Beta-blockers may also be appropriate for some younger people who; are intolerant to ACE inhibitors or ARBs, females who may become pregnant, or where there is evidence of sympathetic drive causing hypertension, e.g. stress.[1] If a beta-blocker is started, then a calcium channel blocker, or an ACE inhibitor/ARB is the preferred second-line treatment.[1]

If peripheral vascular disease is present an ACE inhibitor should be considered to slow disease progression, or a calcium channel blocker to vasodilate the peripheral arteries.

Resistant hypertension

If a patient's clinic blood pressure remains over 140/90 mmHg after a treatment regimen of an ACE inhibitor or an ARB, plus a calcium channel blocker and a diuretic, then the hypertension is considered to be resistant.[1] Patient adherence to treatment should be re-examined and an added emphasis placed on; weight loss, exercise, reduced salt intake, moderation of alcohol intake, stress reduction and minimisation of other medicines that may increase hypertension, e.g. non-steroidal anti-inflammatory drugs (NSAIDs) and oral contraceptives.[15] Secondary causes of hypertension should also be assessed and consultation with a Nephrologist or Cardiologist considered. Ambulatory monitoring of blood pressure should be conducted, where possible, to exclude a white-coat cause for the hypertension and to accurately assess the effects of future and current treatment.[6]

Additional investigations in secondary care may include a renal ultrasound scan, with renal artery Doppler study to investigate stenosis and echocardiogram for ventricular hypertrophy and dilation of the ascending aorta. Measurement of blood renin, aldosterone, cortisol and metanephrine levels may be appropriate, but these tests should be discussed first with an Endocrinologist.[6]

Additional medicines

Further diuretic treatment with spironolactone (25 mg, once daily, in the morning – some clinicians start with 12.5 mg) may be appropriate, if serum potassium is ≤ 4.4 mmol/L.[1] If the patient's renal function is impaired there is an increased risk of hyperkalaemia and hyponatremia. Serum sodium and potassium should be monitored after one week, then every three months for the first year.[12] If the patient's serum potassium is > 4.5 mmol/L consider an increased dose of a thiazide diuretic in preference to spironolactone.[1] An alpha- or beta-blocker may be considered if hypertension continues to be resistant, particularly in males.[1] If the patient is taking optimal, or maximum tolerated, doses of antihypertensive medicines, an appropriate specialist opinion, e.g. Cardiologist if they have cardiovascular disease or Nephrologist if they have declining renal function, is recommended, if this has not been sought already.[1]

New techniques for treating hypertension

Renal sympathetic nerve denervation is a catheter-based technique showing promise in reducing blood pressure in patients with resistant hypertension. After two years, in patients with systolic blood pressures > 160 mmHg, there was an average blood pressure reduction of 32/14 mmHg.[16] Blood glucose levels were also shown to improve.[16] The procedure does not appear to be associated with significant adverse effects. Patients who may benefit from this technique should be discussed with a Cardiologist.

Follow-up and monitoring of people with hypertension

It is important that once hypertension is confirmed, and treatment has begun, that management is intensified over the following three months. Follow-up is also important to ensure target levels are maintained and to reinforce the importance of adherence to the treatment regimen to the patient. Depending on the level of risk and control achieved, medicines should be reviewed on a three to six-monthly basis with surveillance for end organ disease and associated conditions. This provides an opportune time to reinforce lifestyle management and to monitor electrolytes and renal function. Home blood pressure measurements are a useful monitoring adjunct.

Follow-up ambulatory monitoring of blood pressure is helpful when it is difficult to confirm whether target blood pressures are being met, or when additional antihypertensive medicines beyond ACE inhibitors/ARBs, calcium channel blockers or thiazide diuretics are required.

Patients should be advised about the possible adverse effects of their medicines and asked to contact their General Practitioner or Pharmacist if they have any concerns that may affect their adherence to treatment. Dosing regimens should be as simple as possible to maximise adherence and minimise the risk of error.

The New Zealand Formulary provides information on medicine adverse effects and interactions, available from: **www.nzf.org.nz**

Should antihypertensive treatment ever be stopped in older patients?

The average life expectancy for a person aged over 80 years in New Zealand is between eight and ten years and treatment for hypertension can substantially reduce the risk of death in these patients.[17, 18] The Hypertension in the Very Elderly trial (HYVET) treated patients aged over 80 years with hypertension averaging 173/91 mmHg for an average of 1.8 years with indapamide and perindopril to a blood pressure target less

PHO Performance Programme – cardiovascular disease risk assessment

Cardiovascular risk assessment is currently a PHO Performance Programme indicator and should be undertaken at least every five years in the following patient groups in order to count towards the target:[19]

- Males of Māori, Pacific, or Indian sub-continent ethnicity aged 35 – 74 years
- Females of Māori, Pacific, or Indian sub-continent ethnicity aged 45 – 74 years
- Males of any other ethnicity aged 45 – 74 years
- Females of any other ethnicity aged 55 – 74 years

This indicator accounts for 20% of funding; 8% for the total population and 12% for the high needs population.[19] The high needs population for the purposes of the Programme are enrolled people of either Māori or Pacific descent, or people who live in the most deprived socioeconomic areas – NZDep decile 9 or 10.[19]

The programme goal is for 90% of individuals within the target population to have had a CVD risk assessment recorded by 1 July 2014.[19] The target is assessed by counting the number of enrolled people in a PHO within the eligible population who have had a CVD risk recorded since July 2008 (the numerator). This number is then divided by the number of people in the PHO who are eligible for a CVD risk assessment (the denominator).[19] As of 31 December 2012, the nationally reported coverage of cardiovascular risk assessment was 57.8% for the high needs population and 55.8% for the total eligible population.[20] This performance has been steadily trending upwards and 85% of PHOs improved performance for this indicator for the high need population, and 94% improved performance for the total population.[20] However, PHOs will need to make more rapid progress if the performance goal is to be reached before July 2014.

Ensuring that all CVD risk assessments that are taken are recorded in the patient record is one simple way to make progress towards the target.

Further information regarding the PHO Performance Programme is available from: **www.dhbsharedservices.health.nz/Site/SIG/pho/Default.aspx**

than 150/80 mmHg.[11] Stroke rates were reduced by 30%, heart failure mortality by 64% and all-cause mortality by 21%.[11]

There is no reason to withhold antihypertensive treatment from older patients on the basis of age alone and routine treatment of hypertension should generally be offered to the patient for as long as they wish to take it.

Monitoring blood pressure in older patients

Orthostatic hypotension is more common in older patients.[18] Blood pressure should be recorded lying and standing, and treatment targets adjusted to reduce the risk of blood pressure-related falls. All antihypertensive medicines can compound this problem.[18] It may be necessary to conduct regular medicine reviews with older patients and a blood pressure < 130/70 mmHg should be avoided in patients aged over 80 years.[18]

 For further information see: "Managing medicines in older people", BPJ 47 (Oct, 2012)..

ACKNOWLEDGEMENT: In developing this article we consulted two Cardiologists, two Nephrologists and an Epidemiologist for their views, and thank them for their input.

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Ticagrelor – out with the old, in with the new?

Ticagrelor (Brilinta) is a new oral antiplatelet medicine, which has been available, fully subsidised, with Special Authority, since 1 July, 2013. Ticagrelor, co-administered with low dose aspirin, is an alternative to clopidogrel for the prevention of atherothrombotic events in patients with acute coronary syndromes. In most cases, ticagrelor will be initiated in hospital and continued for 12 months after discharge.

Ticagrelor (pronounced *tie-kag-re-lore*), co-administered with aspirin as dual antiplatelet treatment, is indicated for the prevention of atherothrombotic events in adult patients with acute coronary syndromes, such as ST elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (NSTEMI). It is anticipated that for the majority of patients, ticagrelor will be initiated in hospital and then continued in the community after discharge. Patients will qualify under the Special Authority criteria (for the subsidised prescription of ticagrelor) whether they are treated with medical management or revascularisation (e.g. percutaneous coronary intervention or coronary artery bypass grafting) for their acute coronary syndrome.[1, 2]

Special Authority criteria for ticagrelor

The Special Authority criteria for ticagrelor are the same for both an initial application for use in a patient with an acute coronary syndrome (valid for 12 months) and for a second application for a subsequent acute coronary syndrome. Applications are able to be made by any relevant practitioner. Both the initial approval and renewal are valid for 12 months.

Prerequisites:

1. Patient has recently* been diagnosed with an ST elevation or non-ST elevation acute coronary syndrome **AND**
2. Fibrinolytic therapy has not been given in the last 24 hours and is not planned

* "Recently" in the context of this Special Authority is acute coronary syndrome diagnosed within a few days or weeks rather than months.

N.B. Some patients in New Zealand have been taking ticagrelor as part of an AstraZeneca product familiarisation programme, and will continue on this programme.

Evidence of the effectiveness of ticagrelor

Evidence of the effectiveness of ticagrelor comes largely from the PLATO trial.[3] This multicentre, randomised, double-blind trial compared ticagrelor with clopidogrel, both used in combination with aspirin, as dual antiplatelet treatment in 18 624 patients with acute coronary syndromes.

Results from the PLATO trial showed that compared to patients taking clopidogrel, those patients taking ticagrelor, had an absolute risk reduction of 1.9% (relative risk reduction of 16% or an NNT of 54) for the combined primary endpoints of myocardial infarction, stroke and death from vascular causes.[3, 5] This further breakdown of the results showed that patients taking ticagrelor and aspirin, compared with patients taking clopidogrel and aspirin, had a significantly lower incidence of:

- Myocardial infarction (5.8% versus 6.9%)
- Death from vascular causes (4.0% versus 5.1%)
- Deaths from any cause (4.5% versus 5.9%)
- Stent thrombosis (in patients receiving a stent during the study period) (1.3% versus 1.9%)

There was no significant difference in the overall incidence of stroke between the two treatment groups. However, there were more haemorrhagic strokes in patients taking ticagrelor than in those taking clopidogrel (23 [0.2%] versus 13 [0.1%]).[3]

The beneficial effects of ticagrelor compared to clopidogrel were detected within the first month of the study and persisted for the length of the trial.[3] There was no significant difference between the treatment groups in the rate of major bleeding (as defined by the study criteria), and in the rate of fatal or life-threatening bleeding. However, there was an increase in major non-CABG related bleeding in the ticagrelor group and a significant increase in the small number of patients who experienced fatal intracranial haemorrhage, compared with patients in the clopidogrel group.[3]

A change in practice for patients with acute coronary syndromes

Until now, the majority of patients with acute coronary syndromes have been prescribed clopidogrel and aspirin. There is evidence, however, from the Platelet Inhibition and Patient Outcomes (PLATO) trial that patients prescribed dual antiplatelet treatment with ticagrelor and aspirin may be at lower risk of ischaemic events and death when compared to patients taking clopidogrel and aspirin (See: "Evidence for ticagrelor").[3] The 2012 New Zealand guidelines for the management of non-ST elevation acute coronary syndromes recommend ticagrelor, rather than clopidogrel, as the preferred antiplatelet medicine.[4]

How does ticagrelor work?

Ticagrelor reversibly inhibits the platelet adenosine diphosphate (ADP) P2Y12 receptors which results in rapid inhibition of platelet activation and aggregation. Clopidogrel also acts on these receptors, however, because it is a "prodrug", the transformation to the active metabolite tends to result in slower and less consistent inhibition of platelets than with ticagrelor.[3, 5] The transformation of clopidogrel to its active metabolite requires the enzyme CYP2C19. Approximately 30–40% of people of Māori, Pacific and Asian ethnicity have reduced function CYP2C19 polymorphisms, compared to 15% of Europeans.[6] Although it is not yet proven, ticagrelor may be of particular benefit, compared with clopidogrel, for people in these ethnic groups (Māori, Pacific and Asian).

Prescribing ticagrelor

Twice daily dosing is required

Treatment with ticagrelor is initiated with a loading dose of 180 mg (two 90 mg tablets), followed by one 90 mg tablet, twice daily, with or without food. The twice daily dosing may mean that ticagrelor is less preferred for patients who have poor compliance with medicines; clopidogrel is dosed once daily.

Ticagrelor should be co-administered with low dose aspirin, e.g. 100 mg daily (see: "Black box warning", opposite). Treatment with ticagrelor is usually continued for 12 months.[2, 4]

No dose reduction is required for older patients or patients with renal or mild hepatic impairment. If a patient requires elective surgery, it is recommended that ticagrelor be stopped five days prior.[7]

FDA black box warning re: ticagrelor and high dose aspirin

The United States Food and Drug Administration (FDA) released a black box warning stating that ticagrelor should not be used concurrently with doses of aspirin of more than 100 mg daily.[8] This warning was placed because sub-group analysis from the PLATO trial suggested that ticagrelor was of less benefit when used with higher doses of aspirin (> 100 mg daily). However, higher aspirin doses are uncommonly used outside of the United States, and the scientific basis for the warning has been challenged recently in the literature.[8, 9]

Contraindications

Ticagrelor is contraindicated in patients with:[2]

- Active bleeding
- History of intracranial haemorrhage
- Moderate to severe hepatic impairment (due to an absence of data)

There is currently no data on the safety of ticagrelor for patients who have had fibrinolytic therapy within the last 24 hours for a STEMI, as these patients were excluded from the PLATO trial. There is also no clinical data on the safety of ticagrelor in patients on renal dialysis, those with moderate or severe hepatic impairment or in children aged under 18 years.

Cautious use is required in selected patients

Ticagrelor should be used with caution in patients who have an increased risk of bleeding, e.g. after recent surgery or trauma, recent gastrointestinal tract bleeding and coagulation disorders.[2] It should also be used with caution in patients taking medicines that may increase their bleeding risk such as NSAIDs,[2] or patients who have asthma or chronic obstructive pulmonary disease (see: "Adverse effects").

Patients with an increased risk of bradycardia were excluded from the PLATO trial because an earlier study had identified an increase in this type of event.[2, 3] Ticagrelor should therefore be used with caution in patients at risk of bradycardia (e.g. patients with sick sinus syndrome, second or third degree AV block) unless a pacemaker is fitted.

Interactions with other medicines

Ticagrelor is metabolised in the liver primarily by the enzyme CYP3A4, a member of the cytochrome P450 group of isoenzymes. Ticagrelor is also a weak inhibitor of CYP3A4 which has implications for patients who are taking other medicines metabolised by CYP3A4, such as simvastatin. It is recommended that patients taking ticagrelor should not be prescribed more than 40 mg of simvastatin daily as ticagrelor has the potential to increase the serum concentration of simvastatin, which may increase the likelihood of adverse effects from the statin.[2, 10] Smaller increases in plasma concentrations of atorvastatin have been found when taken with ticagrelor, however, these increases are not thought to be clinically significant.[2]

Ticagrelor should not be prescribed if the patient is already taking a CYP3A4 inhibitor such as ketoconazole or clarithromycin. Medicines that induce CYP3A4 enzymes, such as carbamazepine, phenytoin and rifampicin should also be avoided.

Ticagrelor also inhibits a transporter protein, p-glycoprotein (P-gp), which can result in an increase in serum concentration of P-gp substrates such as digoxin and ciclosporin.[11] Because digoxin has a narrow therapeutic range, if ticagrelor is initiated plasma digoxin levels should be monitored.

Limited clinical evidence suggests there is no significant clinical interaction between ticagrelor and proton pump inhibitors (PPIs). In contrast, clopidogrel may be less effective when used in combination with some PPIs, e.g. omeprazole.[6, 12]

Adverse effects

Bleeding – As with all antiplatelet medicines, ticagrelor is associated with an increased risk of bleeding. Overall, ticagrelor is not associated with an increased risk of bleeding when compared to clopidogrel although in the PLATO trial there were higher numbers of non-CABG related major bleeds and, although the numbers were small, a significantly higher number of fatal intracranial bleeds.[3]

Dyspnoea – Patients taking ticagrelor have been found to have an increased risk of dyspnoea compared to patients taking clopidogrel. In the PLATO trial, however, only approximately 1% of patients who developed dyspnoea had to discontinue the medicine for this reason.[3, 13] Most episodes of dyspnoea have been reported to be mild or moderate, transient, self-limiting and likely to occur in first month of treatment.[13] The mechanism underlying the development of dyspnoea is currently unknown, however, it does not appear to be due to aggravation of a pre-existing respiratory or cardiac condition. Although a subgroup analysis of the PLATO study did not find a higher risk of worsened dyspnoea in patients with pre-existing dyspnoea or those at increased risk of dyspnoea, e.g. patients with asthma, COPD or congestive heart failure, ticagrelor should be used with caution in these patients.[2]

Elevations in creatinine and urate – Levels of creatinine and urate were significantly increased in patients taking ticagrelor compared to patients taking clopidogrel in the PLATO trial.[3]

Creatinine – It is recommended that renal function is checked after one month of treatment with ticagrelor and as clinically indicated after that. Patients aged over 75 years, those who have moderate or severe renal impairment and those taking an angiotensin receptor blocker (ARB) may be more at risk of an increase in creatinine levels.[2]

Urate – It is recommended that ticagrelor is used cautiously in patients who have a history of hyperuricaemia or gout. The use of ticagrelor in patients who have uric acid nephropathy is not recommended.[2]

Other adverse effects reported include gastrointestinal disturbances (e.g. nausea, vomiting, diarrhoea, dyspepsia, abdominal pain), dizziness, headache, rash and pruritus.[7]

ACKNOWLEDGEMENT: Thank you to **Dr Mark Webster**, General and Interventional Cardiologist, Auckland DHB for expert review of this article.

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Multiple sclerosis: Managing shades of grey

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system (CNS) resulting in neurological deficits, which can take a variable course. Peak onset occurs between age 20 and 40 years.[1] MS should be diagnosed definitively by a Neurologist, following clinical assessment combined with MRI evidence of typical lesions occurring on separate occasions, in different locations within the CNS. Chronic disability is a feature of MS. The primary care team will co-ordinate care with the patient's partner/family, carer and specialist health professionals, to reduce MS-associated complications and to assist with personal and family adjustment. Disease-modifying medicines may reduce the number of relapses a person with MS experiences, but there is no treatment which is effective at slowing the disease once in the progressive phase.

Prevalence and patterns of multiple sclerosis

Multiple sclerosis (MS) is the most prevalent non-injury related cause of long-term neurological disability in younger adults.[2] The underlying cause of MS has not been established but it is widely considered to be an autoimmune disease, possibly precipitated by an infectious agent priming the immune system against myelin antigens.[3] The factors influencing the prognosis of a person with MS are poorly understood. However, chronic disability is a frequent outcome and this can be devastating as it threatens independence, employment and lifestyle. The condition itself is not usually directly fatal, but death in people with MS is often due to a complication of the condition, e.g. pneumonia or a urinary tract infection (UTI).[1] On average, the life expectancy of people with MS is reduced by six to 11 years.[1]

Epidemiology

In New Zealand in 2006, there were almost 3000 people identified as having MS.[4] Approximately 2700 of these people were European, 90 identified as Māori, and 15 of Pacific Island or Asian descent.[4]

MS has a peak age of onset between 20 and 40 years and like other autoimmune diseases it is 2.5 times more prevalent among females than males.[3] However, males who develop MS will often be more severely affected by disability.[3]

MS is generally more common with increasing distance from the equator. This effect has been observed in both northern and southern hemispheres.[4] In New Zealand there is a three-fold increase in prevalence from 35°S (North) to 48°S (South).[4] This effect is approximately three times stronger in females than males.[4] The reason for this is unknown, however, there is increasing evidence that low vitamin D levels in regions with less sunshine exposure may be one of several contributing factors.[5]

One in five people who develop MS has an affected relative and 4% of people with a first-degree relative with MS will develop the disease.[1]

Smoking and exposure to the Epstein-Barr virus later in life are also associated with increased incidence of MS.[6]

Patterns of multiple sclerosis

MS is characterised by inflammatory demyelination (damage to the myelin sheath of the neuron), which occurs within the white and grey matter of the CNS.[6] The peripheral nervous system is unaffected. Inflammation causes a loss of myelin and neuronal/axonal injury. Over time, remyelination can repair some of this damage. Plaques are formed from dense clusters of supporting cells (gliosis) surrounded by fibrous material. The location, frequency and balance of injury versus repair determines the pattern of MS and its associated disability.

MS has a highly unpredictable course and prognosis. Communicating this uncertainty can be a challenge for clinicians and result in anxiety for patients and their families. After a period of months to years a cycle of recurrent symptoms may develop that allows a pattern of MS to be identified. The pattern of MS that a person has will affect their prognosis and may influence the treatment of their condition.

MS typically begins with a sudden episode of neurological symptoms. For example, the patient may report blurring of vision in one eye (optic neuritis), double-vision (diplopia), unsteadiness, sensory impairment spreading upwards from the legs or dysfunction in the limbs.[3] The symptoms are characterised by increasing severity over days, then stabilisation over days to weeks, followed by gradual resolution which will be complete or partial after several weeks.[7] The first episode is often referred to as a "clinically isolated syndrome".[7] Later, following a second clinical episode, or subclinical changes on MRI (see: "The McDonald Criteria". Page 42), the patient may be diagnosed with relapsing-remitting MS.

Relapsing-remitting MS is the pattern seen in 85% of people with early-stage MS.[1] This is characterised by recurrent acute neurological episodes, referred to as relapses, with residual symptoms suddenly increasing, or new symptoms developing. Recovery is gradual although residual symptoms will often remain.[7] Overall, people with MS have approximately one relapse every two years, however, the frequency and severity vary widely.[8] A high frequency of attacks during the first two years of MS is linked to and increased likelihood of people with relapsing-remitting MS developing secondary progressive MS and long-term disability.[8]

Secondary progressive MS develops in two-thirds of people with relapsing-remitting MS, within 15 years of diagnosis.[1] This is a gradual, progressive worsening of neurological function that is independent of acute relapses and due to a low-grade degenerative process which leads to most of the long-term disability in people with MS. However, acute attacks may still occur during this phase.[1]

"Benign MS" occurs in approximately one in ten people with MS.[1] This is diagnosed following a period of ten to 20 years without significant disability.[1, 7] However, many patients do still develop disability and the value of this diagnosis is controversial.

Primary progressive MS occurs in one in ten people with MS.[1] Neurological symptoms develop insidiously and progressively from the outset, usually with slowly increasing spastic lower limb weakness (paraparesis).[6]

Diagnosing multiple sclerosis

General Practitioners should consider MS as a possible diagnosis when a person aged 20 – 50 years presents with symptoms and signs suggestive of a focal CNS deficit. In this situation, a neurological referral should be considered. Diagnosis of MS is confirmed by the presence of characteristic lesions on MRI (see: "The McDonald criteria").

A focused clinical history should be taken whenever MS is suspected. Transient neurological symptoms in the past may assist in diagnosis. Clinical features are also likely to vary between patients.[1]

People who develop MS may report positive and/or negative symptoms. Positive symptoms include muscle spasm, and one in five people with MS will have various forms of neuralgia (e.g. tingling/burning/pruritic sensations), in the skin of the limbs, trunk or face.[3, 7] An electric shock sensation down the spine when the neck is flexed (Lhermitte's symptom) is characteristic, but not specific, for MS.[3] Negative symptoms include visual disturbances (e.g. decreased visual acuity or diplopia), numbness, motor dysfunction (e.g. weakness, gait disturbances and ataxia), bladder dysfunction, bowel or erectile problems.[6]

People with MS may experience a transient worsening of symptoms due to heat, e.g. when exercising, bathing or when in a heightened emotional state; this is known as Uhthoff's symptom.[7]

Optic neuritis and MS are closely linked. Visual impairment due to optic neuritis is the reason why one-quarter of people with MS present to a clinician, and more than half of people who present with optic neuritis will eventually develop MS.[1] Like MS, optic neuritis is more prevalent among younger women, Europeans and in people who live further from the equator.[9] However, there are alternative diagnoses that should also be considered, and people with optic neuritis will not necessarily develop MS.

The clinical features of optic neuritis are impairment of visual acuity, usually with reduced colour vision and eye pain, especially on eye movement.[9] Swelling of the optic disc (papilloedema) may also be observed. An important sign is a relative afferent pupillary defect. This can be detected with the "swinging light test". When a light is shone into the unaffected eye, both pupils constrict. However, when the light is swung to the affected eye, both pupils appear to dilate (also known as paradoxical dilation). This is because damage to the optic nerve on the affected side impairs reflexive pupillary

constriction. Loss of colour vision out of proportion to the visual acuity loss is also a characteristic feature of optic neuritis. To detect red desaturation, ask the patient to compare the intensity of a bright red object between each eye. Ishihara plates (images used to test red-green colour deficiencies with coloured numbers within patterns), if available, can detect a reduction in colour perception in 88% of patients with optic neuritis.[9]

After an attack of optic neuritis the optic disc may appear pale, compared to the unaffected eye, suggesting optic atrophy. Typically, vision will improve over time which helps to differentiate the episode from a progressive cause of impaired visual acuity, e.g. glaucoma.

The differential diagnosis for optic neuritis includes ischaemic optic neuropathy, inflammatory optic neuropathies due to infection, e.g. syphilis, cat scratch disease, or non-infectious conditions, e.g. sarcoidosis, and compressive optic neuropathies, e.g. tumours, thyroid eye disease.[9] Ischaemic optic neuropathy usually occurs in people aged older than 50 years, pain is usually absent and loss of vision may be more acute and profound.[9]

Internuclear ophthalmoplegia in MS is caused by damage to neuronal connections in the brainstem between the abducens (VI) and oculomotor (III) cranial nerve nuclei.[10] This prevents the eyes working as a single functioning unit and affects horizontal gaze. When the patient looks laterally to the unaffected side there is impairment of adduction observed in the affected eye, which lags behind the unaffected eye, as shown in Figure 1.[11] Fast involuntary movements (nystagmus) of the unaffected abducting eye are also often seen.

An extensor plantar (Babinski) response may be seen in people with MS without other major signs of upper motor neurone dysfunction.[7]

Differential diagnosis of MS

People with MS often receive an alternative diagnosis before the correct one is established; most frequently a musculoskeletal injury for males or a psychiatric cause for females.[7] Conditions that may need to be considered, depending on the presenting features, include:[7]

- Psychiatric disorders/functional syndromes
- Other causes of visual impairment
- Sciatica and musculoskeletal injury
- Carpal tunnel syndrome and other peripheral nerve disorders
- Intrinsic or expanding lesions of the CNS, e.g. tumour, syringomyelia
- Motor neurone disease
- Infections, e.g. syphilis, HIV or spinal abscess
- Systemic inflammatory disorders, e.g. systemic lupus erythematosus
- Stroke
- Paraneoplastic syndromes

MS only affects the upper neurone pathways in the CNS therefore absent reflexes or muscle wasting are not usually seen in patients with MS.[7]

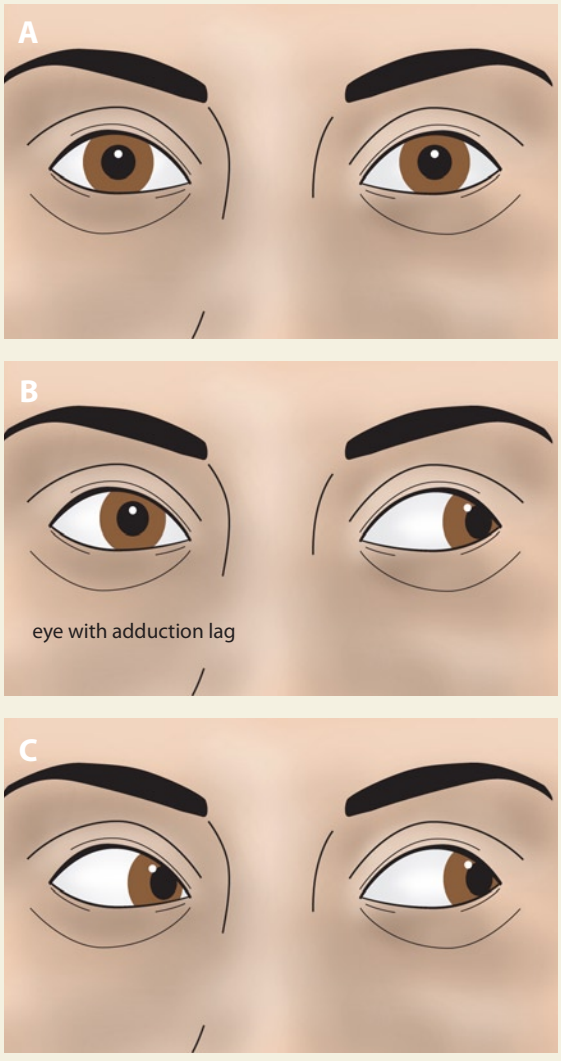

Figure 1: Adduction lag in unilateral internuclear opthalmoplegia on rapid left gaze. Starting at position A, adduction lag can be seen at position B, virtual complete adduction can be seen at position C. Adapted from Prasad and Galetta, 2010.[10]

The McDonald criteria

The McDonald clinical criteria state that a diagnosis of MS requires two or more episodes of inflammatory demyelination to occur on separate occasions, at least 30 days apart, in different locations within the CNS.[12] However, in some patients separation in time and space can be established with a single MRI scan when there is reasonable historical evidence of a prior attack.[12] An important aspect of the criteria is that alternative explanations for the lesions have been reasonably excluded.[12]

Multiple sclerosis and pregnancy

Females diagnosed with MS are often of childbearing age and may therefore have questions relating to their ability to have children. MS does not affect fertility.[1] Relapses are less likely to occur during pregnancy, but are more common in the three to six months following delivery.[1] Overall, pregnancy does not have any effect on the course of MS. Disease-modifying medicines should be avoided during pregnancy and ideally, for at least three months prior to conception.[13]

Confirmatory investigations are usually performed in secondary care

Primary care plays a key role in identifying people suspected of having MS. Confirmatory investigations are usually undertaken by a Neurologist. An MRI of the brain is the investigation of choice. Additional testing is generally only requested when there is uncertainty about the diagnosis.[3]

MRI is reported to have a sensitivity of 95% for detecting clinically confirmed MS.[6] The number of lesions found on MRI may also be the most accurate predictor of clinical outcome.[3] The patient's history often underestimates disease severity and other asymptomatic CNS lesions will be detected on MRI in approximately 80% of people with MS after they experience their first clinical episode.[3] People with spinal and brainstem lesions are at greater risk of permanent disability.[3]

Visual evoked potentials may identify subclinical demyelination of the optic nerve.[7] However, these findings can be non-specific and may be normal in half of people with MS.[3]

Oligoclonal IgG bands in cerebrospinal fluid present on protein electrophoresis are found in up to 95% of people with well established MS. [7] However, protein electrophoresis of the cerebrospinal fluid is rarely required where a characteristic clinical history and MRI changes are present.

Disease-modifying treatment of multiple sclerosis

Patients with active relapsing-remitting MS may be treated with disease-modifying medicines. There are three such medicines for MS available in New Zealand under Special Authority; glatiramer acetate, interferon beta-1a and interferon beta-1b. Subsidy for these medicines requires application from a Neurologist to the Multiple Sclerosis Treatment Assessments Committee. The subsidy approval criteria include that the patient has frequent relapses and significant residual disability. The medicines are sent by courier directly to patients or clinicians (i.e. not dispensed from a pharmacy). General Practitioners may assist in monitoring for adverse effects in patients taking these medicines.

The medicines have complex actions on immune function and their mechanism in MS is uncertain. They are considered to be immune-modulators, rather than general immune-suppressors. All three medicines have similar, limited effects on the course of relapsing-remitting MS: an approximate one-third reduction in the frequency of relapses, with a

greater effect on the reduction of new lesions and a less consistent effect on slowing the progression of disability.[14, 15] None of these medicines appear to be effective in people with secondary progressive MS.[15, 16]

Glatiramer acetate (Copaxone) is available in 20 mg prefilled syringes which are injected subcutaneously, once daily. Adverse effects of treatment include hypersensitivity reactions within minutes of injection, nausea, constipation, syncope, depression, headache, tremor and back pain.[13]

Interferon beta-1a (Avonex) is available in 30 micrograms vials and prefilled syringes and pens which are injected intramuscularly, once a week.[13] **Interferon beta-1b** (Betaferon) is available in 250 micrograms vials, with a reconstituting solvent, and is injected subcutaneously, every second day.[17] Beta-interferon may cause influenza-like symptoms and occasionally vomiting.[13] Less common adverse effects include anaphylaxis, urticaria, personality changes and suicidality, convulsions, hepatitis and thyroid dysfunction.[13] Dose titration may be necessary to improve tolerability.

Managing relapses and symptoms of multiple sclerosis

People with MS require the care of a multidisciplinary team. This is usually co-ordinated by primary care and supported in some regions by specialist nurses. The goals of treatment are to improve the quality of life, reduce symptoms and to minimise any adverse effects of treatment. Where possible, people with MS are encouraged to manage their own well-being.[19] The closest adult family member of a person with MS is often their main carer and supporting this relationship is an important role of the multidisciplinary team. The rate of divorce is nine times higher among couples where one person has MS.[7]

The Multiple Sclerosis Society of New Zealand is a non-profit organisation that provides support, education and advocacy for people and families with MS. For further information see: **www.msnz.org.nz**

Acute relapses are managed with methylprednisolone

Relapses are more common in people with MS who have viral infections or who are undergoing major life events causing stress.[7] Influenza vaccination of both the person with MS and their carer may reduce the likelihood of MS relapses and minimise the risk of respiratory complications.[7]

MS relapses can be treated in primary care with oral methylprednisolone in doses up to 200 mg, daily, following

New disease-modifying medicines for multiple sclerosis

Monoclonal antibodies which target specific surface molecules of immune cells have been trialled as MS-modifying injectable medicines. **Natalizumab** is available in New Zealand for the treatment of relapsing-remitting MS. It is not currently subsidised on the Pharmaceutical Schedule. One 300 mg intravenous infusion is given every four weeks.[13] Natalizumab reduces relapses by approximately two-thirds and new MRI lesions by 90%, with a small risk of serious viral neurological disease (progressive multifocal leukoencephalopathy) due to reactivation of John Cunningham virus (a common polyomavirus).[18]

There are four other monoclonal antibodies, mainly indicated for the treatment of leukaemia or prevention of organ transplant rejection, that have been trialled in the United States as disease-modifying medicines for MS; alemtuzumab, daclizumab, ocrelizumab and ofatumumab.[18] However, evidence of effectiveness for the treatment of MS is inconclusive and some of these medicines have been withdrawn from clinical use.

Fingolimod, teriflunomide, dimethylfumarate and laquinimod are oral medicines that have been investigated for the treatment of relapsing-remitting MS.[18] Fingolimod (Gilenya) is the only one of these medicines approved for use in New Zealand, and none are subsidised. Fingolimod is available in 0.5 mg capsules, taken once daily.[13] Fingolimod is contraindicated in people who are immunosuppressed, or have active infections or malignancies.[13] Adverse effects include; transient bradycardias and heart block, hypertension, diarrhoea, weight loss and a range of respiratory and neurological adverse effects.[13]

consultation with a Neurologist.[13] However, higher intravenous or oral doses (500 mg – 1 g, once daily, for three to five days) of methylprednisolone may be recommended if the patient is severely debilitated.[19] The treatment regimen will be guided by the Neurologist, and may also include a tapering period over 10 – 12 days.[13] Using corticosteroids more than three times a year or for periods longer than three weeks should be avoided.[19]

Symptomatic control of multiple sclerosis involves a multi-disciplinary approach

If the condition or needs of a patient with MS change, consider the following points:[1]

- Is there an alternative explanation? e.g. tiredness could also be explained by anaemia, hypothyroidism or depression
- Could a virus or other infection be the trigger?
- Are the symptoms an adverse effect of treatment?
- Are the symptoms explained by the gradual progression of MS?

Management of symptoms usually involves consultation with other members of the multi-disciplinary team. Check the New Zealand Formulary for medicines information and subsidy status.

Fatigue is experienced by 85% of people with MS.[1] Muscle weakness and ataxia may also be present. Depression, poor sleep, inadequate nutrition and pain should all be considered as possible contributing factors. Exercise, e.g. walking, should be encouraged. Physiotherapy will often improve motor control after two or three sessions and may allow exercise goals to be increased.[1] Both aspirin and amantadine (an antiviral and antiparkinson medicine) have been shown to provide some benefit for treating fatigue in patients with MS, however, further trials are required before the extent of any clinical effect can be established.[20, 21]

Pain affects up to two-thirds of people with MS.[1] Musculoskeletal pain can be caused by restricted movement or muscle spasms.[1] Peripheral pain can be managed with analgesics and physiotherapy. CNS lesions may also cause pain, especially if there are lesions affecting sensory pathways, e.g. trigeminal neuralgia may occur due to brainstem inflammation.[1] Table 1 lists medicines for the treatment of chronic pain.

Bowel dysfunction, e.g. constipation and/or faecal incontinence affects over 60% of people with MS.[1] This can be highly detrimental to the patient-carer relationship and is a common reason why people with MS are admitted to residential care.[1] Fluid and fibre intake should be increased before a laxative is considered.[1] Overflow incontinence, secondary to constipation, should also be considered as a possible cause.

Patients with MS may have difficulty initiating their bowel movement. Digital rotatory stimulation of the anorectum can be performed by a carer to provoke rectal contraction and bowel emptying.[22] If digital stimulation is ineffective then suppositories, e.g. bisacodyl (10 mg) or glycerol (3.6 g) in the morning, are recommended.[22]

Loperamide is the first-line treatment for faecal incontinence in patients with MS. For example, begin with 4 mg, daily, then adjust until control is achieved - the maintenance dose is 2 – 12 mg, daily, in one to three divided doses.[13, 22] Anal plugs can also be effective in patients with faecal incontinence.[22]

Table 1: Medicines that may be considered for chronic pain

Medicine	Dose
Amitriptyline or nortriptyline	10 – 75 mg, once daily
Carbamazepine (especially for trigeminal neuralgia)	100 mg, once or twice daily, increased gradually according to response, with a usual dose of 200 mg, three or four times daily, and up to 1.6 g daily in divided doses in some patients
Gabapentin	Titrate in 300 mg steps to a maximum of 3.6 g daily in three divided doses; a common dose in patients with MS is 600 mg, three times daily (do not withdraw abruptly)

Bladder problems, e.g. urgency, nocturia, incontinence and UTIs are common in people with MS. Anti-cholinergics, e.g. oxybutinin, 5 mg, three times daily, reduce urinary urgency and frequency.[1] However, these medicines can cause incomplete bladder emptying and urinary self-catheterisation may be required if there is significant post-voiding urine remaining.[1] If oxybutinin is ineffective or not tolerated, tolterodine (2 mg, twice daily) or solifenacin (5mg, once daily, increased to 10 mg, once daily, if necessary) may also be considered (under Special Authority).[13]

Nocturia can be treated with desmopressin.[1] The nasal spray is subsidised if prescribed by a Neurologist and injections are available on Special Authority. Tablets are available, but unsubsidised. Desmopressin can be taken at bedtime for nocturia, but can also be used during the day, e.g. for long journeys, however, it should only be taken once in a 24 hour period.[1]

Spasticity and spasms frequently occur in people with MS and affect mobility. Physiotherapy in combination with passive exercise is used to prevent permanent muscle shortening. Table 2 lists medicines for the treatment of severe spasticity.

Cannabidiol plus tetrahydrocannabinol oromucosal spray is an adjunctive treatment for moderate to severe spasticity in adults with MS.[13] This medicine is not subsidised and requires Ministerial approval as it is a controlled drug. Cannabidiol is contraindicated in people with a personal or family history of psychosis or a history of other severe psychiatric disorder.[13]

Managing disability and wider affects of MS

Managing disability is central to the care for a person with MS. An important component is to ensure that the patient feels that their needs are being met. Walking sticks and walking frames reduce the risk of falls and devices such as an hinged ankle-foot braces can improve dorsiflexion and improve movement.[3] Agreed goals are important in managing disability; these should be ambitious and challenging, yet achievable.[19]

Cognitive impairment occurs in approximately half of all people with MS, e.g. reduced ability to learn, plan or concentrate.[1] This is related to brain atrophy, particularly in areas near the cortex or in association fibres that link different brain areas.[1] A medicine review should be conducted to ensure adverse effects are not a contributing factor and the patient

Table 2: Medicines that may be considered for severe spasticity

Medicine	Dose
Baclofen	5 mg, three times daily, increased at three day intervals by 5 mg, three times daily. The maintenance dose is 30 – 80 mg daily, in three divided doses.
Orphenadrine citrate (for acute muscle spasm)	100 mg, twice daily
Dantrolene	25 mg, once daily, increased after four to seven days to 25 mg, two to four times daily. Doses can be increased further by 25 mg, every four to seven days, to a maximum of 100 mg, four times daily.
Diazepam	2 – 15 mg, daily, in divided doses, increased to 60 mg, daily, according to response
Fampridine*	10 mg, orally, twice daily, approximately every 12 hours, with treatment reviewed after eight weeks
Tizanidine (unapproved medicine)	2 mg, once daily, increased by 2 mg, daily, according to response, at intervals of at least three to four days, to a maximum daily dose of 36 mg, daily, in three to four divided doses

* Fampridine (Fampyra) is a potassium channel blocker indicated for improving walking in adults with MS. One month free trial is available in New Zealand, however, ongoing treatment is expensive and not subsidised in New Zealand.

Driving a motor vehicle

Driving ability should be considered once a person with MS has residual disability. Patients should be assessed for vision, limb strength, accuracy of rapid foot movements and joint proprioception.[23] Driving should cease if there are doubts regarding a person's ability to control a vehicle.[23]

Where there is uncertainty regarding a person's ability to drive, it may be appropriate to seek the assistance of an occupational therapist with experience in driver assessments. MS has a variable and intermittent progression, so it may be necessary to restrict people from driving during periods of relapse, while allowing them to drive during periods of remission.[23] License conditions may include regular assessments, such as an annual medical report.[23]

The New Zealand Transport Agency has a "Medical aspects of fitness to drive" website available from: **www.nzta.govt.nz/resources/medical-aspects/2.html**

assessed for sleep disturbances and depression. Restless leg syndrome is more common in people with MS and a sleep study may be useful in identifying causes of daytime fatigue.[1]

Depression and/or anxiety are likely to be experienced by people with MS, and also carers or family members.[1] Over half of people with MS will have a major depressive episode and the rate of suicide is reported to be 7.5 times higher in people with MS.[1] The patient, their carer and family require opportunities to talk about the impact MS is having on them as well as having input into how positive change can be made. Referral for counselling is recommended.

Lifestyle interventions in people with MS

Diet should be reviewed in patients with continual weight loss or evidence of malnutrition. It is possible that there are additional benefits to improving nutrition in people with MS, and some guidelines suggests that a diet rich in sunflower, corn, soya and safflower oils may slow disease progression, however, the evidence for this is not strong.[7] The "Swank Diet" is gaining popularity in Australasia, largely due to the fact that it is being promoted by a clinician who himself has MS. The diet is low in saturated fat and high in vegetables, but there is currently no controlled evidence of benefit.

People with MS may be concerned about their vitamin D intake. The increased incidence of MS with increasing distance from the equator is the main reason behind such thinking. People who wish to increase their intake of vitamin D can be advised to spend more time in direct sunlight. During winter, eating more oily fish, e.g. salmon or cod liver oil, will also increase vitamin D intake. If there is ongoing concern about vitamin D deficiency, cholecalciferol 1.25 mg, once a month, is an appropriate supplement.[13]

For further information see: "Vitamin D supplementation: Navigating the debate", BPJ 36 (June 2011).

ACKNOWLEDGEMENT: Thank you to **Dr Ernie Willoughby**, Neurologist, Auckland DHB, Senior Lecturer, Department of Medicine, University of Auckland and Patron and Medical Advisor, Multiple Sclerosis Society of New Zealand for expert review of this article.

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Using NSAIDs with allopurinol in gout

Dear Editor.

[Re: "An update on the management of gout", BPJ 51, Mar 2013] Would you really give NSAIDs continuously while starting and titrating allopurinol? If someone starts at 50 mg and has a target dose of 300 mg, they would be on NSAID continuously for six months if we followed your suggestion of increasing 50 mg per month. It seems a long time to expose someone to the risks associated with NSAIDs. Why not just treat flare ups if they occur?

Dr Stephen Hoskin
General Practitioner
Te Anau

It is recommended that low-dose non-steroidal anti-inflammatory drugs (NSAIDs), e.g. naproxen 250 mg, twcie daily, or colchicine be co-prescribed with allopurinol to prevent rebound flares of gout while serum urate levels are being lowered. This is because urate-lowering treatment for gout is frequently associated with gout flares, and this relationship is reported to persist for the first 6 – 12 months of treatment.[1, 2] This paradoxical effect is thought to be due to rapid lowering of serum urate levels causing crystals previously precipitated in tissues to become activated. This causes activation of cyclooxygenase-2 expression (Cox-2), subsequent prostaglandin production and the classical symptoms of gout flare.[1]

Recommendations for the duration of prophylaxis differ in guidelines, ranging from one month to one year.[1] However, analysis of three randomised, placebo-controlled trials concluded that naproxen was well tolerated and that six months of prophylactic treatment was found to provide greater benefit, compared to two months of treatment, with no associated increase in adverse effects.[1]

Therefore, the consensus opinion is that a low-dose NSAID (or another suitable medicine if NSAIDs are not appropriate for an individual patient) should be continued while titrating allopurinol, for as long as it takes to achieve the target serum urate level of ≤ 0.36 mmol/L, and in some cases this may be up to six months.

Further evidence to support the use of anti-inflammatory prophylaxis during urate lowering treatment also includes the following:[3]

- A patient may be asymptomatic but there can be ongoing chronic inflammation (i.e. no flare but ongoing damage to joints)
- The use of a prophylactic medicine can reduce both the incidence and severity of flares
- If flares are not controlled, there is a risk of decreased adherence to urate-lowering treatment and consequently the potential for ongoing uncontrolled disease (e.g. development of polyarticular disease and tophi)

The patient's age and co-morbidities should be considered when choosing a prophylactic medicine, e.g. the presence of chronic kidney disease or a history of gastrointestinal bleeding. A NSAID, therefore, may not always be the appropriate choice. Low dose colchicine (0.5 mg, once or twice daily) is an alternative for some patients, although care is still required (e.g. a further reduction in dose) when it is used in patients with impaired renal function.[3]

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Appropriate use of antibiotics

Dear Editor

[Re: "Cold season in primary care", BPJ 52, Apr 2013] The suggestions about when to use antibiotics are very subjective. One could argue that symptoms are "significant or severe" for every patient we see, otherwise they wouldn't have bothered to spend the time and money coming to see us. How do you define "high risk"? The infection is "not resolving" by when? How do we differentiate "infection" from post infective symptoms such as a lingering cough?

Dr Stephen Hoskin,
General Practitioner
Te Anau

The decision whether or not to prescribe antibiotics for patients with upper respiratory tract infections (URTI) is complex and, as with any primary care decision, is likely to be based on both objective and subjective reasoning.

There has been extensive research on antibiotics in URTI, with a view to reducing inappropriate antibiotic use and, therefore, the growth of antibiotic resistance. A 2013 Cochrane systematic review concluded that antibiotics were of no benefit in patients with acute URTI, and were associated with adverse effects.[1] However, despite this research, clinical guidance cannot always be prescriptive because a guidance document will never be able to account for all the variables present in every clinical contact. Therefore, we rely on clinicians being able to interpret each individual patient-doctor interaction and come to the most appropriate decision for that patient.

We agree that whenever a patient presents, the problem they have on that day is usually regarded as "significant and severe" for them. The patient's perception of their symptoms is very relevant, however, it is the role of the clinician to objectively evaluate the significance of the patient's symptoms and signs, while also taking into consideration other factors such as patient age, relevant past history, social history and the presence of co-morbidities, when formulating a diagnosis, assessing risk and making treatment decisions. Patients with factors such as a significant past history of chronic obstructive pulmonary disease (COPD) or bronchiectasis, frail elderly people and those who are immunodeficient are considered at high risk of complications from URTI.

Clinicians will have a general idea of the usual course of a URTI, based on their experience and observation of other patients, and can judge if the infection is not resolving in the expected time, or if symptoms are increasing or worsening in severity. There is clearly a grey area between acute and chronic symptoms, as the latter always begins as the former, but again, clinical judgement is necessary. Post-infective symptoms such as lingering cough in an otherwise well person can be differentiated from infection, in which the patient's signs and symptoms are worsening in severity and they remain generally unwell.

Consensus guidance on appropriate antibiotic use for common infections seen in primary care is available in the updated Antibiotic Guide accompanying this edition of the journal. We would welcome feedback from clinicians on how they resolve the "to give an antibiotic or not" dilemma and their strategies on how to balance the benefit and risk for an individual with the wider goal of reducing inappropriate antibiotic use.

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