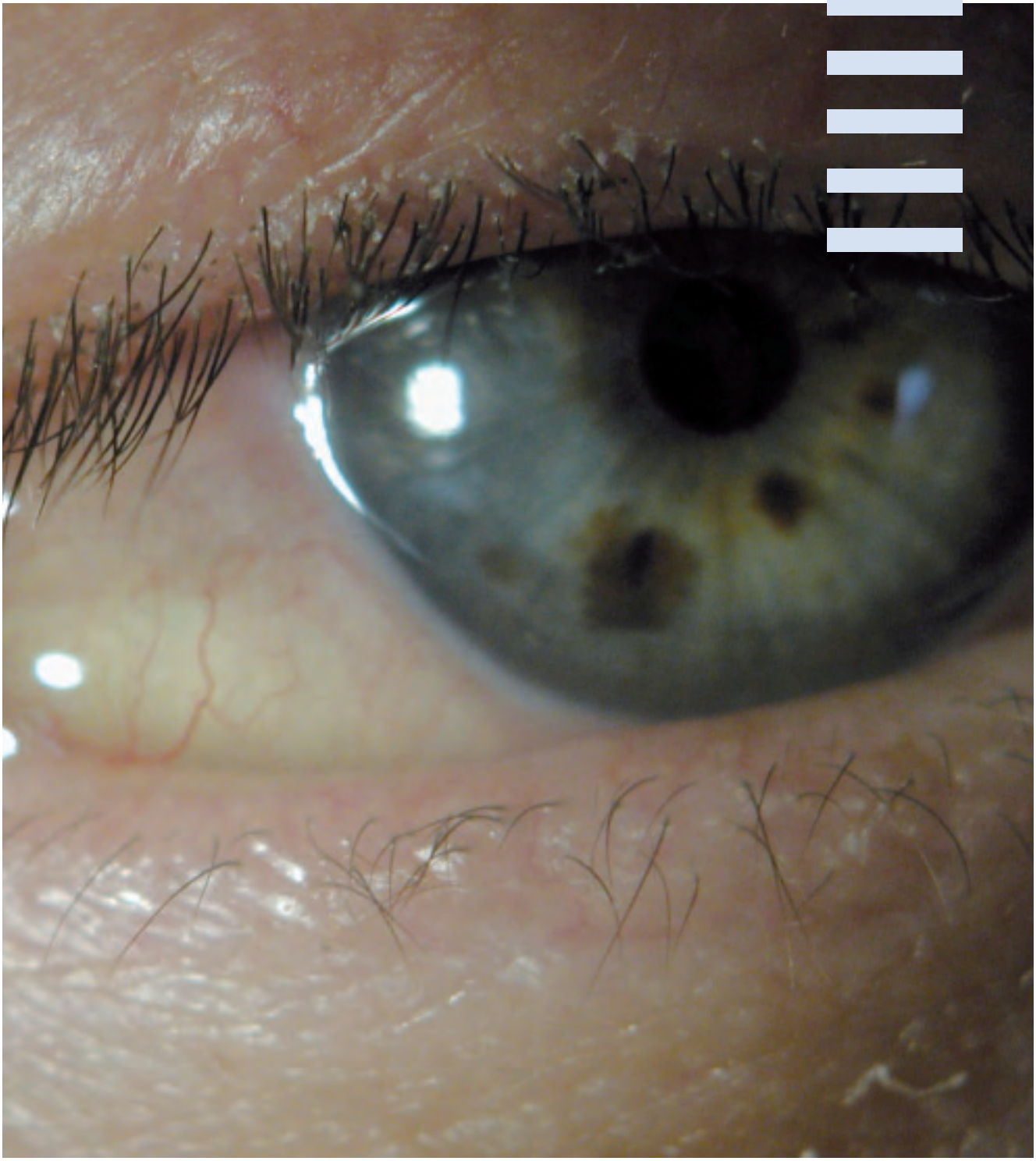
Supplement to
AUSTRALIAN OPTOMETRY

Special issue ALLERGY

# pharma

September 2010



- Diabetic retinopathy
- Allergic conjunctivitis
- Allergy and keratoconus
- Peripheral corneal ulcers
- Ocular nutrition
- Recurrent corneal erosions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**Indication:** Treatment of neovascular (wet) age-related macular degeneration (AMD). 0.5 mg or 0.3 mg is recommended to be administered by intravitreal injection once a month. **Dosage and administration:** Recommended dose is 0.5 mg (0.05 mL) or 0.3 mg (0.03 mL) given monthly. Interval between doses should not be shorter than 1 month. Treatment might be reduced to one injection every 3 months after the first three injections but, compared to continued monthly doses, dosing every 3 months may lead to an approximate 5-letter (1-line) loss of visual acuity benefit, on average, over the following 9 months. Patients should be evaluated regularly. Must be administered by a qualified ophthalmologist using aseptic techniques. Broad-spectrum topical microbicide and anaesthetic should be administered prior to injection. Patient should self-administer antimicrobial drops four times daily for 3 days before and after each injection. Not recommended in children and adolescents. **Contraindications:** Hypersensitivity to product components, active or suspected ocular or periocular infections, active intraocular inflammation. **Precautions:** Intravitreal injections have been associated with endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract. Proper aseptic injection techniques must be used. Monitor patients during the week following injection to permit early treatment if an infection occurs. Intraocular pressure and perfusion of the optic nerve head must be monitored and managed appropriately. Safety and efficacy of administration to both eyes concurrently have not been studied. There is a potential risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors. A numerically higher stroke rate was observed in patients treated with ranibizumab 0.5mg compared to ranibizumab 0.3mg or control, however, the differences were not statistically significant. Patients with known risk factors for stroke, including history of prior stroke or transient ischaemic attack, should be carefully evaluated by their physicians as to whether Lucentis treatment is appropriate and the benefit outweighs the potential risk. As with all therapeutic proteins, there is a potential for immunogenicity with Lucentis. *Lucentis has not been studied in patients with concurrent eye conditions such as retinal detachment or macular hole.* No formal interaction studies have been performed. Should not be used during pregnancy unless clearly needed; use of effective contraception recommended for women of childbearing potential; breastfeeding not recommended. Patients who experience temporary visual disturbances following treatment must not drive or use machines until these subside. **Side effects:** Very common: Intraocular inflammation, vitritis, vitreous detachment, retinal haemorrhage, visual disturbance, eye pain, vitreous floaters, conjunctival haemorrhage, eye irritation, foreign body sensation in eyes, lacrimation increased, blepharitis, dry eye, ocular hyperaemia, eye pruritus, intraocular pressure increased, nasopharyngitis, headache, arthralgia. Common: Retinal degeneration, retinal disorder, retinal detachment, retinal tear, detachment of the retinal pigment epithelium, retinal pigment epithelium tear, visual acuity reduced, vitreous haemorrhage, vitreous disorder, uveitis, iritis, iridocyclitis, cataract, cataract subcapsular, posterior capsule opacification, punctuate keratitis, corneal abrasion, anterior chamber flare, vision blurred, injection site haemorrhage, eye haemorrhage, conjunctivitis, conjunctivitis allergic, eye discharge, photopsia, photophobia, ocular discomfort, eyelid edema, eyelid pain, conjunctival hyperaemia, stroke, influenza, urinary tract infection*, anaemia, anxiety, cough, nausea, allergic reactions (rash, pruritus, urticaria, erythema). Uncommon: Blindness, endophthalmitis, hypopyon, hyphaema, keratopathy, iris adhesions, corneal deposits, corneal oedema, corneal striae, injection site pain, injection site irritation, abnormal sensation in eye, eyelid irritation. Rare but serious adverse reactions related to intravitreal injections include endophthalmitis, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract. (luc020610m.doc)

**Please note changes to Product Information in italics.*

1. Brown MM, et al. Can J Ophthalmol. 2005;40:277-287. 2. Williams RA, et al. Arch Ophthalmol. 1998;116:514-520. 3. Rosenfeld PJ, et al. N Engl J Med. 2006;355:1419-1431. 4. LUCENTIS Approved Product Information. 5. Brown DM, et al. Ophthalmol. 2009;116:57-65. 6. Chang TS, et al. Arch Ophthalmol. 2007;125:1460-469.

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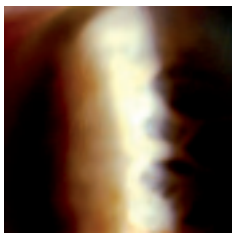
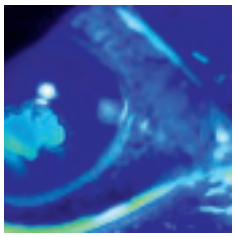
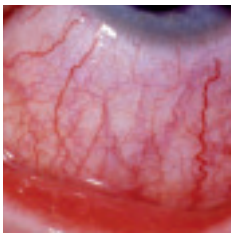
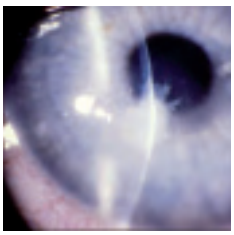
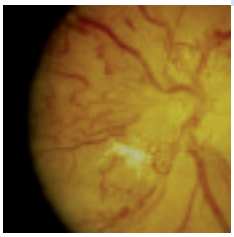



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# Diabetic

## Screening and early detection

**Dr Tim Gray** MBBS
Medical Retina Consultant
Ophthalmologist
Lyell McEwin and Royal
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**Diabetic retinopathy (DR) is the most common cause of irreversible blindness in the working population of those between 20 and 70 years of age.**

With the current epidemic of diabetes, prevention of blindness from this condition will rely increasingly more heavily on shared care arrangements between optometrist, ophthalmologists, general practitioners, endocrinologists and hopefully, government-funded education and screening programs.

Treatment of this condition is going through a renaissance with multiple studies demonstrating a benefit of anti-vascular endothelial growth factor (anti-VEGF) therapy. As always, the most important aspect of DR management is prevention and early detection prior to onset of visual impairment. The purpose of this paper is to provide an overview of diabetic retinopathy with an emphasis on a new, albeit familiar classification system and recent trials in the prevention and treatment of diabetic retinopathy.

## Epidemiology

There are two main forms of diabetes. Type 1 diabetes has an early onset, usually before 30 years of age, and requires treatment with insulin at onset of disease for patient survival. Type 2 diabetes has a later onset and can often be treated by dietary restrictions and exercise, but many patients eventually require oral hypoglycaemic agents and sometimes insulin. Type 1 patients more frequently suffer severe ocular complications but because type 2 diabetes accounts for 90 to 95 per cent of all cases of diabetes, these patients comprise the majority who develop visually threatening disease.

In Australia an estimated 15.6 per cent of the population over 25 years of age have diabetes, of whom 7.9 per cent have diabetic retinopathy.[1] Therefore about 1.2 per cent of this population have diabetic retinopathy.

The most common cause of vision impairment in diabetic retinopathy is diabetic macular oedema (DMO). Other causes include macular ischaemia, vitreous haemorrhage and tractional retinal detachment from proliferative diabetic retinopathy.

- Best corrected visual acuity
- Test for a relative pupil defect if visual acuity is impaired
- Examine for rubeosis iridis
- Intraocular pressure
- Gonioscopy if IOP elevated
- Dilate with tropicamide 0.5% or 1%
- Examine lens for cataract, particularly if vision impaired
- Indirect ophthalmoscopy with slitlamp plus/minus retinal photographs

**Table 1. Ocular examination of patients with diabetes**

| Proposed disease severity level | Findings observable on dilated ophthalmoscopy |
|---|---|
| No apparent retinopathy | No abnormalities |
| Mild NPDR | Microaneurysms only |
| Moderate NPDR | More than just microaneurysms but less than severe NPDR |
| Severe NPDR | Any of the following and no signs of proliferative retinopathy:<br>More than 20 intraretinal haemorrhages in each of four quadrants<br>Definite venous beading in two or more quadrants<br>Prominent IRMA in one or more quadrants |
| PDR | One or both of the following:<br>Neovascularisation<br>Vitreous/preretinal haemorrhage |

IRMA: intraretinal microvascular abnormalities; NPDR: non-proliferative diabetic retinopathy; PDR: proliferative diabetic retinopathy
Reproduced with permission from Wilkinson CP, Ferris FL 3rd, Klein RE et al. Proposed international clinical diabetic retinopathy and diabetic macular edema severity scales. *Ophthalmology* 2003; 110: 1679.

**Table 2. International clinical diabetic retinopathy disease severity scale**

## Aetiology

Diabetes affects almost every aspect of metabolism within the vasculature. Microscopically, the earliest feature is loss of pericytes, which usually surround and support the endothelium of the retinal capillaries.[2] This results in increased leakage of protein as well as blood and damage to the endothelium. As a consequence of endothelial damage and alterations of platelet metabolism, blood is more likely to clot, resulting in ischaemia. Retinal ischaemia results in the production of VEGF which stimulates neovascularisation.

## Risk factors for retinopathy progression

Poor glycaemic control has been consistently shown to worsen prognosis in the long term. The Diabetes Control and Complications Trial randomly assigned 1,441 patients with insulin dependent diabetes to either conventional or intensive insulin treatment and their progress was followed for four to nine years.[3] In the first 18 months of follow-up the intensively treated cohort had a greater risk of progression, but after four years there was about a five-fold reduction

# retinopathy
## can prevent 90% of vision loss

in the risk of progression.

The reason for the early worsening of retinopathy is not fully understood and usually it is not visually threatening if no or mild retinopathy exists. When moderately severe NPDR or worse retinopathy exists, there is an increased risk of complications and patients should be monitored more closely–two monthly until the improvement in haemoglobin A[1]C stabilises.

Hypertension and to a lesser extent hyperlipidaemia is associated with a greater risk of diabetic retinopathy progressing. Intensive management of hypertension in the United Kingdom Prospective Diabetes Study has been demonstrated to slow this progression.[4] Controlling hyperlipidaemia is particularly important in patients with substantial hard exudates.

Pregnancy accelerates DR so these patients should be screened every trimester.[5]

### Ocular examination in patients with diabetes

All patients with diabetes should be examined before and after pupil dilation (Table 1). Pupil dilation increases the sensitivity of screening by more than 50 per cent. Prior to mydriasis it is important to test best corrected visual acuity, intraocular pressure and the iris for rubeosis iridis. If there is a reduction in visual acuity, use the swinging flash light test to check for a relative afferent pupil defect.

Following mydriasis, examination of the lens for cataract and then fundus with slit-lamp biomicroscopy is performed. During fundoscopy the macula is examined firstly for DMO, then the optic disc for neovascularisation at the disc (NVD), peripheral retina to assess presence, and severity of retinopathy and vitreous for haemorrhage.

### Retinal imaging in patients with diabetes

The current NHMRC guidelines in the management of diabetic retinopathy recommend non-mydriatic (or mydriatic) retinal photographs to screen for DR when access to a dilated fundus examination by a trained examiner is not available. There have been multiple publications, including a systematic review of the literature, that have found mydriatic retinal photographs to have a greater sensitivity yet adequate specificity when compared with dilated fundus examinations.[6,7]

The gold standard for diabetic retinopathy screening is dilated, stereoscopic retinal photographs in which seven overlapping photographs are taken as per the ETDRS trial.[8]

A single 45 degree mydriatic retinal photograph has a sensitivity of 90 to 96 per cent and specificity of 87 to 98 per cent.[7,9] Non-mydriatic photographs are less sensitive but if used should encompass two or three fields: posterior pole, temporal and nasal fields.[9,10,11]

A single non-mydriatic retinal photograph is not ideal and can miss 75 per cent of cases of PDR.[6] By relying solely on non-stereoscopic retinal photographs you have a risk of missing macular oedema, which is not always associated with hard exudates, and peripheral retinal pathology, and they are less accurate for detecting glaucomatous optic neuropathy.

Optical coherence tomography has been proven to be as accurate as a dilated stereoscopic fundus examination by a retinal specialist and is extremely useful in diagnosing mild diabetic macular oedema and monitoring response to treatment.[12]

Fundus fluorescein angiogram is useful in guiding macular laser photocoagulation of clinically significant macular oedema and picking up early proliferative diabetic retinopathy.

### Classification

The classification system outlined in Tables 2 and 3 is based on data from the Early Treatment Diabetic Retinopathy Study (ETDRS) and was proposed by Wilkinson and colleagues in 2003.[13] There has recently been a push for this to be adopted more widely

**Continued page 4**

| **Proposed disease severity level** | **Findings observable on dilated ophthalmoscpy** |
|---|---|
| Diabetic macular oedema apparently absent | No apparent retinal thickening or hard exudatives in posterior pole |
| Diabetic macular oedema apparently present | Some apparent retinal thickening or hard exudatives in posterior pole |

**If diabetic macular oedema present, it can be categorised as:**

| **Proposed disease severity level** | **Findings observable on dilated ophthalmoscopy** |
|---|---|
| Diabetic macular oedema present | Mild diabetic macular oedema: some retinal thickening or hard exudates in posterior pole but distant from the centre of the macular |
| | Moderate diabetic macular oedema: retinal thickening or hard exudates approaching the centre of the macula but not involving the centre |
| | Severe diabetic macular oedema: retinal thickening or hard exudates involving the centre of the macula |

Hard exudates are a sign of current or previous macular oedema. Diabetic macular oedema is defined as retinal thickening; this requires a three-dimensional assessment that is best performed by dilated examination using slitlamp biomicroscopy and/or stereoscopic fundus photography.
Reproduced with permission from Wilkinson CP, Ferris FL 3rd, Klein RE et al. Proposed international clinical diabetic retinopathy and diabetic macular edema severity scales. *Ophthalmology* 2003; 110: 1680.

**Table 3.International clinical diabetic macular oedema disease severity scale**

# Diabetic retinopathy

**From page 3**

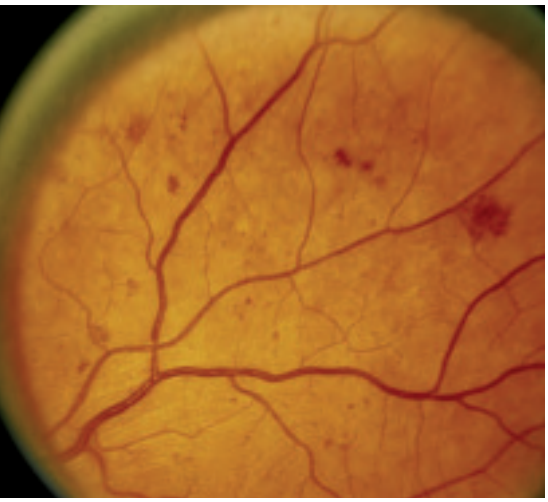

**Figure 1. Example of microaneurysms and retinal haemorrhages. If present to this extent in four quadrants, this fits the definition of severe non-proliferative DR.**

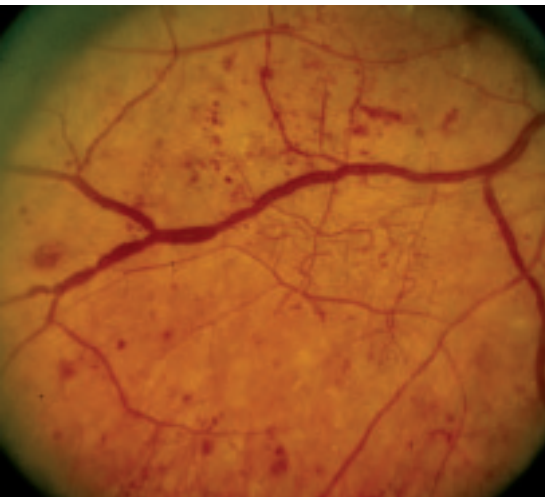

**Figure 2. Example of venous beading and an IRMA in the centre of the image**

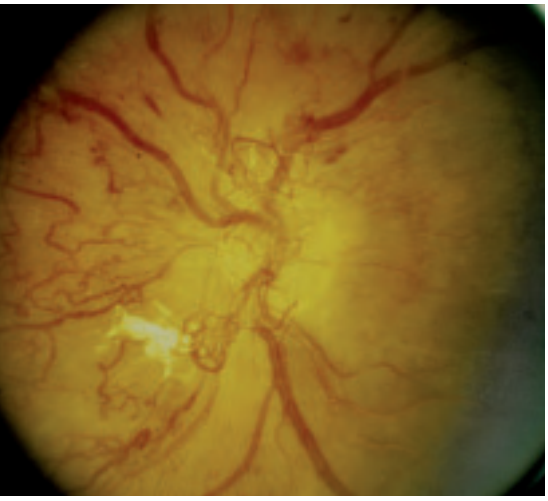

**Figure 3. Neovascularisation at the optic disc (NVD)**

in Australia. It is hoped that this simplified classification will be adopted world-wide to enable exchange of information and data between countries and between the broad range of health-care practitioners involved in caring for diabetic patients. In addition, such a classification is useful in determining who will benefit most from treatment and how frequently to follow up with patients.

Figure 1 is taken from the ETDRS to assist in the classification of severe non-proliferative diabetic retinopathy. If there are microaneurysms and retinal haemorrhages to the extent or worse than that depicted in Figure 1 in four quadrants of the retina, then it would be classified as severe NPDR. Figure 2 is an example of venous beading and if present in two or more quadrants it would be considered severe NPDR. Figure 2 also has an example of an intraretinal microvascular anomaly (IRMA). An IRMA may be due to intraretinal new vessel growth or dilated pre-existing vessels. IRMA can be difficult to differentiate from early neovascularisation classic of PDR but the latter will increase in size with time if untreated. Figure 3 is an example of neovascularisation at the optic disc. In 69 to 73 per cent of cases of PDR have new vessels at the disc.

## Frequency of diabetic retinopathy screening

Table 4 outlines the suggested duration between follow-up consultations based on the above severity classification. This is based on the NHMRC guidelines for the management of diabetic retinopathy 2008.[5]

## Management

One of the most important aspects of managing patients with diabetic retinopathy is notifying the general practitioner or endocrinologist of the extent of disease. There is likely to be a genetic predisposition in some patients developing early complications of apparently well-controlled diabetes while other patients with poorly controlled diabetes suffer little. Identifying DR is crucial in predicting likelihood of developing other complications of diabetes and enables tighter control of risk factors such as blood sugar levels, hypertension and hyperlipidaemia.

The recent FIELD[14] and ACCORD-Eye[15] studies have demonstrated a benefit in the use of fenofibrate, 200 milligrams per day in diabetic patients. The group of patients treated with this lipid-lowering drug was 30 per cent less likely to require laser treatment for diabetic retinopathy than the group receiving placebo. This benefit was above and beyond any protection gained simply from lowering cholesterol levels and was particularly beneficial when used in combination with another lipid-lowering drug, simvastatin. Patients who already had diabetic retinopathy were less likely to progressively worsen when treated with fenofibrate.

Patients with severe NPDR, PDR, DMO or any unexplained loss of vision should be referred to an ophthalmologist experienced in managing diabetic retinopathy.

## Treatment of diabetic macular oedema

The ETDRS study[8] proved the beneficial effects of macular laser photocoagulation in preventing visual loss from DMO. Patients with clinically significant macular oedema (CSMO) have the most to gain. CSMO is defined as either any retinal thickening within 500 micrometers of the centre of the fovea, hard exudates within 500 micrometers of the centre of the fovea when adjacent to retinal thickening or retinal thickening of one disc diameter in size within one disc diameter of the centre of the fovea. If left untreated, these patients had a 24 per cent chance of moderate visual loss (loss of three lines of vision) over a period of three years. When treated with gentle focal laser to microaneurysms or grid pattern of laser to diffuse retinal thickening, the risk of moderate visual loss reduced to 12 per cent.

Intravitreal triamcinolone has been demonstrated to be of benefit in patients who fail to respond to macular laser but there is a high risk of ocular hypertension and cataract formation from this steroid agent.[16]

More recent studies have demonstrated a benefit of intravitreal anti-VEGF therapy.[17] The BOLT study was a small randomised controlled trial from the UK that looked at patients who had failed to respond to laser therapy for DMI. One group of patients received bevacizumab (Avastin) intravitreal injections six-weekly and another group received further laser plus a sham injection. Over 12 months the group treated with bevacizumab improved 10 letters with an average of nine injections compared with one line improvement in the laser group. Bevacizumab is used off-label (not approved

by the Therapeutic Goods Administration) in Australia for this use, mainly when DMO has not responded or is not amenable to laser therapy.

Ranibizumab (Lucentis) has been studied by the Diabetic Retinopathy Clinical Research Network in the USA.[18] A large randomised controlled trial compared monthly injections of ranibizumab plus prompt or deferred laser, sham injection plus prompt laser or four milligram intravitreal triamcinolone plus prompt laser. The ranibizumab group gained nine letters of vision over 12 months regardless of whether they received prompt or deferred laser. The triamcinolone plus laser group gained four letters and the sham plus laser group gained three letters. Ranibizumab is not yet available for this use in Australia.

In patients with persistent diabetic macular oedema despite adequate laser and evidence of vitreomacular traction on OCT, pars plana vitrectomy may help reduce the retinal thickening and improve visual acuity.

## Proliferative diabetic retinopathy treatment

The Diabetic Retinopathy Study (DRS)[19] and ETDRS[8] were both large randomised controlled trials that demonstrated a significant benefit of pan-retinal photocoagulation in preventing severe visual loss (< 5/200). PRP reduced the risk of severe visual loss by more than 50 per cent. A subgroup of patients with high-risk characteristics was at greatest risk of developing visual loss and show signs of any of the following features:

- neovascularisation at the disc (NVD) of greater than one-third disc area
- any neovascularisation at the disc or within one disc diameter of the disc with vitreous or pre-retinal haemorrhage
- neovascularisation elsewhere (NVE) greater than one-half disc area in extent associated with vitreous or pre-retinal haemorrhage. These patients had a 26 per cent chance of severe visual loss in two years if untreated compared to 11 per cent if treated with prompt PRP.

The ETDRS study determined that patients with less severe PDR or severe NPDR also benefited from PRP but the risk of severe visual loss without treatment was less at 3.6 to seven per cent in two years. Patients with CSMO and PDR should have their CSMO treated prior to PRP unless high-risk characteristics are present, in which case both macula laser and PRP should be administered promptly.

Vitrectomy was proven by the Diabetic Retinopathy Vitrectomy Study[20] to be of benefit, particularly in type 1 diabetic patients with slow to resolve vitreous haemorrhage. In addition, it is commonly performed for tractional retinal detachment recently involving the macula, combined tractional and rhegmatogenous retinal detachment, progressive fibrovascular proliferation and rubeosis iridis with vitreous haemorrhage preventing adequate laser. Intravitreal bevacizumab is commonly injected one week prior to vitrectomy to reduce the risk of postoperative vitreous haemorrhage.

| Condition | Follow-up frequency/management |
|---|---|
| Type 1 diabetic | 1 - 2 yearly from 5 years of onset |
| Type 2 diabetic | 1 - 2 yearly from diagnosis |
| Mild NPDR | 12 monthly |
| Moderate NPDR | 6 - 12 monthly |
| Severe NPDR | 2 - 4 monthly, sometimes PRP |
| DMO | 2 - 4 monthly, consider focal/grid laser |
| Proliferative DR | 2 - 4 monthly, PRP |

PRP = panretinal photocoagulation

**Table 4. Diabetic retinopathy screening frequency and management**

## Conclusion

Diabetic retinopathy is becoming an increasing problem because of our ageing population and prevalence of diabetes in the community. Systematic screening and early treatment can prevent vision loss by an estimated 90 per cent. Improved management of diabetes, hypertension and hyperlidaemia is crucial, as is timely laser photocoagulation in clinically significant macular oedema and proliferative diabetic retinopathy. Intravitreal anti-VEGF therapy, triamcinolone and vitrectomy are useful treatment options in refractory cases.


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# Abstracts

**Dr Laura Downie**
PhD BOptom PGCertOcTher
DipMus(Prac) AMusA

## Pollen attack

Conjunctival irritation in proven non-allergic patients during pollen season has been linked to the destruction of tear fluid proteins and damage to human conjunctival cells by pollen proteases.

During pollen seasons, allergy-like symptoms can be observed in proven non-allergy sufferers. An examination was performed on the proteolytic activity of two aggressive pollen species: hazelnut (Corylus avellana) and birch pollen (Betula pendula). Cultivated conjunctival cells (CHANG cells) were incubated with pollen extracts and the cytomorphological changes were analysed.

Pollen proteases were found to destroy tear fluid proteins. Pollen-treated CHANG cells had a statistically significant decrease in cell viability that was related to the pollen extract concentration and the incubation period.
*Dev Ophthalmol* 2010; 45: 83-92

## Corneal graft survival

Local treatment with alpha-melanocyte stimulating hormone (alpha-MSH) significantly reduces corneal allorejection in an *in vivo* experimental graft model.

Alpha-MSH is a neuro-peptide that suppresses host inflammatory defence mechanisms. The study involved orthotopic corneal transplantation, with recipients receiving subconjunctival alpha-MSH or sham injections twice-weekly. Grafts were assessed for up to 70 days, with graft inflammation and opacification compared between groups.

There was a significant increase in corneal graft survival in alpha-MSH treated recipients compared with controls. Graft infiltration studies also demonstrated a significant decrease in the number of mononuclear and polymorphonoculear cells in the alpha-MSH treated group.
*Transplantation* 2009; 88: 2: 180-187

## Ocular immune privilege lost

An animal model has shown that ocular sympathetic nerves are critical for the generation and maintenance of ocular immune privilege.

Researchers surgically removed the superior cervical ganglion, which supplies sympathetic fibres to the eye, and investigated the immune response generated against exogenous antigens and allogenic tumour cells. Without functional sympathetic fibres, the eye lost the ability to prevent both the immune rejection of intraocular tumour cells and the suppression of delayed-type hypersensitivity responses against soluble antigens injected into the anterior chamber.

These findings suggest that immune privilege is lost in the absence of functional ocular sympathetic innervation, allowing immune responses to become exaggerated.
*Am J Pathol* 2009; 175: 3: 1218-1225

## Anatomical deficiencies

Japanese researchers have reported an association between myopic refractive error and allergic conjunctivitis.

External allergens are recognised as the primary causative factor in allergic disease but little is known about the influence of internal factors, such as the biometric structures of the eye.

Patients were divided into four groups: contact lens wearers with established allergic conjunctivitis, contact lens wearers without allergic conjunctivitis, non-contact lens wearers with allergic conjunctivitis, and asymptomatic non-contact lens wearers.

In spectacle wearers, the refractive spherical equivalent and spherical power were significantly lower in patients with allergic conjunctivitis than in patients without allergic conjunctivitis. No significant differences were evident between the contact lens wearing populations.
*Eye* 2009; 23: 1: 63-66

## Topical drugs' itchy outcome

Cutaneous allergy testing may be useful for detecting clinically-relevant allergy to eye medications.

In this retrospective study, 90 patients suspected of an allergic reaction to topical pharmaceuticals—as indicated by symptoms of itching and conjunctival hyperaemia—underwent skin allergy testing. Cutaneous testing revealed an allergy to eye medication in 36 per cent of patients tested, which was described to be the causal factor in 22 cases. The most frequent medication-associated allergies were directed against tobramycin, neomycin sulfate and thimerosal.
*Ophthalmic Res* 2009; 41: 4: 225-229

## Spray it away

The intra-nasal corticosteroid, mometasone furoate nasal spray (MFNS) is effective in reducing ocular symptoms in patients with seasonal allergic rhinitis (SAR).

A total of 429 patients with moderate to severe baseline symptoms of SAR were randomised to MFNS treatment (200 mcg/day) or placebo treatment. Subjects evaluated the severity of their ocular symptoms each morning and night over 15 days. A significant reduction in eye itching, burning and watering were observed for the MFNS group versus placebo.
*J Allergy Clin Immunol* 2010; 125: 6: 1247-1253.

## Pathogens link to conjunctivitis

A study identified a link between chronic allergic conjunctivitis and latent ocular infection.

A five-year, prospective, non-randomised trial involved the evaluation of 236 patients (472 eyes) with a history of allergic conjunctivitis but no clinical signs of infection. Conjunctival scrapings were examined cytologically. Latent concurrent infection was identified in 37 per cent of eyes. The main pathogens included Candida albicans, Staphylococcus epidermidis and Chlamydia trachomatis. The incidence of concurrent infection was strongly correlated with the percentage of eosinophilic cells.

The authors concluded that pathogens can stimulate activation of eosinophils with a consequent worsening of the severity and chronicity of allergic symptoms.
*Cornea* 2009; 28: 8: 839-842

## Risk of corneal graft rejection

Allergic airway hyper-reactivity (AAH) has been identified as an important risk for corneal allograft rejection. Corneal grafts transplanted into hosts with allergic conjunctivitis are known to experience an increased incidence and more rapid immune rejection compared with allografts transplanted to non-allergic hosts.

In this study, AAH was induced in an experimental animal model, with either ovalbumin or short ragweed extract prior to penetrating keratoplasty. Compared with controls, the AAH-affected group demonstrated a quicker and higher incidence of graft rejection. The mechanism underlying this effect was reported to be a delayed-type hypersensitivity response.
*Am J Transplant* 2009; 9: 5: 1017-1026

# Best solution for ortho-K wear

**Paul Milford**
BScOptom

If a blinking eyelid flushes away the chemicals found in disinfecting solutions, what happens at night when the patient goes to sleep?

**Do ortho-K contact lenses need a specialised solution for cleaning and disinfection? Aren't they just gas permeable hard contact lenses? The truth is, choosing the best solution requires careful consideration.**

Over recent years hard contact lens use has declined and so too has the variety of hard contact lens solutions. For patients, availability of the recommended solution is limited as not all outlets sell all available products. This provides us as the contact lens prescriber with the opportunity to recommend and supply the best possible product for our ortho-K patients.

The Boston brand of hard lens solutions, which has been available for many years, works well with the Boston XO lens material. The Capricornia BE, Australian Contact Lens Emerald lens and the Gelflex Tab Nightmoves ortho-K lenses all use the Boston XO material. Menicon recommends using Menicare Plus solution with its Menicon CRT lenses.

## Rubbing

As with any contact lens, daily rubbing of ortho-K lenses is essential. Inserting a dirty lens into the eye will increase the risk of allergies, irritation and infections, and lead to an increase chance of drop-out. A daily cleaning solution such as the Boston daily cleaner provides a better clean than rubbing with a multipurpose solution or saline, although I believe rubbing with saline is sufficient for successful wear. I stress to my patients that they need to rub both the front and back surfaces of the lens each day.

## Disinfection

The Menicare Plus, Boston Conditioning, Boston Simplicity or the AMO Total Care solutions are recommended for chemical disinfection and then insertion into the eye. They have a viscous wetting agent that cushions the lens onto the eye and helps the immediate wetting of the contact lens *in situ*. For daytime wear of hard lenses, the lens is inserted in the morning and chemicals are then flushed away as the eyelid blinks repeatedly throughout the day.

With ortho-K lenses the opposite occurs. The patient places the lens on the eye before closing the eyes to sleep. This has the effect of bathing the cornea with disinfecting chemicals for a period of about eight hours. I have seen patients with toxic epithelial changes from the chemical disinfecting solutions when used with ortho-K lenses.

There are two ways of averting this toxic reaction from the disinfecting chemicals. You can soak the lens in chemical disinfection then rinse the lens just before insertion with either sterile saline solution or a preservative free eye lubricant such as Refresh or Celluvisc minims. A second option, which I believe is preferable, is to use hydrogen peroxide disinfection such as AOSept or Oxysept, whereby you are inserting saline into the eye instead of the disinfecting chemicals.

## Protein removal

Protein build-up on the ortho-K lens will reduce its corneal correcting power and decrease comfort, so it needs to be closely monitored. Menicon has the Progent system in which you add bottle A with bottle B and soak the lens for 20 minutes. This is a very effective method of removing protein from the lens but my concern is that if the patient places the Progent directly into their eye, it may cause permanent scaring to the cornea.

Other protein removal tablets are available such as AMO Total Care and Boston Liquid Enzyme Cleaner. My preference is the Oxysept Ultrazyme protein tablets, which work in conjunction with the hydrogen peroxide solution to effectively remove the protein.

## Annual lens replacement

I recommend annual replacement of ortho-K lenses. This avoids a long-term build-up of protein, distortion of the aged lens, surface scratching and rough chipped lens edges. The lens can be saved as a back-up in case the patient loses or breaks a new lens. With annual replacement, the protein removal process becomes less important so I usually recommend protein removal only if I see significant protein build-up before the 12 months have expired.

## Simple and easy ortho-K lens wear

Patient compliance is generally poor so we need lens care systems that are both easy to use and effective. It is best to rub and rinse with preserved saline followed by AOSept disinfection and annual lens replacement. As with all systems on the market, each has its own limitations. Only daily disposable ortho-K lenses would overcome these issues but I cannot imagine this becoming reality for a long time. ■

**Ernest L Bowling**
USA optometrist and educator
OD MS FAAO Dipl

# More than

When prevention is impractical and a cure is not feasible, managing the symptoms becomes more important

**Ocular allergy is a common hypersensitivity disorder that affects 15 to 20 per cent of the population in developed nations.**[1]

The disorder can be divided into several categories: seasonal and perennial allergic conjunctivitis (SAC/PAC), atopic keratoconjunctivitis (AKC), vernal keratoconjunctivitis (VKC) and drug-induced allergic conjunctivitis (DIAC). Giant papillary conjunctivitis (GPC) is often included among these classifications but GPC results from a chronic mechanical irritation and is not true allergy.

SAC and PAC are the most common presentations, representing more than 95 per cent of all ocular allergy cases.[1]

Mast cell degranulation and histamine release are the cornerstones of the pathophysiology of ocular allergy. IgE antibodies affix to mast cell membranes, and the interaction between allergen and mast cell-bound IgE leads to mast cell degranulation, release of histamine and other inflammatory mediators producing symptoms.[2] Histamine has been shown to be the only mediator that can reproduce the full spectrum of allergic signs and symptoms when instilled in the eye.[3]

The itching histamine induces is the most telling diagnostic clue in identifying a patient with SAC. As the old saying goes: if it itches, then it's allergy. Beyond this key symptom, other presenting symptoms include conjunctival oedema, redness, tearing and eyelid swelling. Clinical signs include a milky or pale pink conjunctiva with vascular congestion that may progress to conjunctival chemosis.[4] A white exudate may form during the acute state, becoming stringy in the chronic form. The cornea is rarely affected, with blurry vision being the most common corneal symptom.[5] Small vascularised nodules (papillae) are prominent on the superior palpebral conjunctiva. Dark circles may occasionally appear beneath the eyes, a result of venous congestion, and are called 'allergic shiners'.[6]

The first step in treating the patient with ocular allergy is to avoid the offending agent. This is not a practical solution as in many cases the cause cannot readily be identified and this practice could mean avoiding the outdoors or family pets. Cold compresses and artificial tears are non-specific therapies. Multiple topical pharmacologic agents are available for treating ocular allergies including antihistamines, mast-cell stabilisers, combination topical antihistamines and mast cell stabilisers, non-steroidal anti-inflammatories (NSAIDs) and corticosteroids.[1,7] Oral antihistamines may be helpful in moderate to severe cases.[7]

## Severe ocular allergy

Atopic keratoconjunctivitis (AKC) and vernal keratoconjunctivitis (VKC) are severe, chronic forms of ocular allergy; combined they represent less than five per cent of ocular allergy cases.[1]

- **Atopic keratoconjunctivitis**

AKC is a chronic inflammatory process associated with a family history of atopy such as eczema and asthma.[8] Association with specific microbes such as *staphylococcus aureus* is suspected.[9,10] AKC typically occurs in males, beginning as early as the teenage years, although it most commonly affects patients aged between 30 and 50 years.[1]

Expect about 25 per cent of elderly patients who have eczema to develop some component of AKC.[4] Ocular signs and symptoms of AKC include intense pruritis (itching), tearing and oedematous, coarse and thickened eyelids.[4] The symptoms are more severe than those in SAC or PAC and are present throughout the year. Seasonal exacerbations, especially in Summer and Winter, are reported in many patients, as is exacerbation from exposure to animal dander, dust and certain foods.[11,12,13] Severe AKC is associated with complications such as blepharoconjunctivitis, cataract, corneal disease and ocular herpes simplex.[14]

Chronic ocular inflammation, which causes significant conjunctival hyperemia and oedema, is a key to diagnosis, along with intense itching. Limbal papillae and Trantas' dots may become evident.[1]

The chronicity of the disease can lead to added conjunctival effects, including cicatrisation, symblepharon and subepithelial fibrosis. The cornea often becomes involved with the presentation of punctuate keratitis, corneal erosions, neovascularisation, and the potential for corneal ulceration or AKC-related shield cataracts.[1]

- **Vernal keratoconjunctivitis**

Vernal keratoconjunctivitis is the second form of rare but severe ocular allergy. Males are also more affected in this disease but at a younger age than those with AKC, with VKC typically occurring between three and 25 years of age.[1] The typical course of the disease entails symptomatic presentation prior to puberty followed by a lessening of symptoms as the patient ages, with complete resolution of the disease during the patient's third decade of life.[4] The symptoms of VKC are at their worst from Spring to Autumn and include severe itching, tearing, photophobia and mucous discharge induced by non-specific stimuli, such as exposure to wind, dust, bright light, hot weather or physical exertion associated with sweating.[11]

Although VKC is considered a form of ocular allergy, more than 50 per cent of patients will have negative skin tests to allergens.[14] Patients with VKC have been shown to have a histaminase deficiency.[16] The lack of this histamine-degrading enzyme

# an itch

potentiates the effects of histamine, worsening the clinical presentation in these patients.

The most impressive clinical finding in VKC sufferers is giant cobblestone papillae on the upper tarsal conjunctiva.[17] Patients may also display a thin, copious milky-white secretion, limbal or gelatinous yellowish-white points (Horner's points and Trantas' dots), an extra lower eyelid crease (Dennie's line), corneal ulcers or pseudomembrane formation.[19] The continuous ocular inflammation can cause further damage including delayed healing, corneal neovascularisation, scarring and amblyopia.[8]

## Differentiating two diseases

The diagnosis of both AKC and VKC involves obtaining a complete medical and familial history of atopy, which is particularly important in identifying AKC where the majority of cases have a personal or familial history of atopy.

The time of presentation also helps differentiate the two diseases. VKC presents in younger patients but AKC occurs later when patients are in their 20s or 30s. VKC is most severe in Summer whereas AKC is more perennial in nature.

The location of papillae can also aid in the differential diagnosis. In VKC papillae are found most often in the superior conjunctiva while in AKC they are often found inferiorly.[7] Treatment of both AKC and VKC is directed at alleviating the severe symptoms, maintaining vision and minimising the side-effects of therapy.

## Therapeutic treatment

Therapeutic options for these disease processes are the same as for other forms of ocular allergic disease. Local corticosteroid therapy has the greatest therapeutic impact but may be associated with localised ocular complications including elevated intraocular pressure, viral infections and cataract formation. Loteprednol etabonate, a modified corticosteroid, is highly effective in the acute and prophylactic treatment of allergic eye disease.[17] This is unavailable in Australia but flurometholone may used as an alternative. The concurrent use of cromolyn sodium with topical steroid therapy is the most effective treatment for VKC according to one study.[18] Cyclosporine 0.05%, such as Restasis, twice a day should be considered if the condition is not responding to other therapies.[4]

Drug-induced allergic conjunctivitis (DIAC) is a reaction to the use of a pharmaceutical agent applied to the eyes or the periorbital region. Ocular ointments, with their prolonged contact time in the eye, are a particular cause but the condition may result from cosmetics, eye-drops, contact lens solutions or any substance. Use of neomycin is a commonly reported causative agent.[20] Preservatives such as thimerosal and benzalkonium chloride are also major culprits.[21]

Stinging and burning of the eyes and itching of the eyelids are the most common complaints. Clinically the condition appears as a beefy red-colored conjunctiva, possibly accompanied by chemosis. The area affected is particularly helpful in making the diagnosis, with signs often localised to the lower lid and inferior conjunctiva, as this is where the instilled medication pools and has the longest contact time. Contact dermatoconjunctivitis may accompany the ocular signs.

Additional ocular signs may include diffuse corneal pinpoint keratitis and conjunctival scarring, as well as papillae and follicle development.[8] A detailed medication history must be garnered to learn the identity of any possible causative agent. The list should include any over-the-counter medications and cosmetics. The earlier the culprit is identified, the more quickly the effects can be halted. Non-preserved artificial tears, four to eight times a day may be beneficial.[7] Topical corticosteroids may accelerate recovery. Saline compresses and steroid lotions are helpful to the skin lesions.[22]


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# Risk is greater for

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**Allergies affect a significant number of our population. It is estimated that up to 25 per cent of the American population suffer from allergic diseases[1] and it is likely that Australia has a similar profile. Ocular symptoms are thought to occur in up to 40 to 60 per cent of those affected by allergies.**[2]

Studies have shown that patients with keratoconus have significantly higher rates of atopy (35 per cent) compared to a control group (12 per cent).[3] Asthma is also significantly higher in patients with keratoconus (18 per cent) compared to a control group (one per cent).[4]

Allergic conjunctivitis refers to a collection of hypersensitivity disorders that affect the lid, conjunctiva and cornea. The clinical presentation can be divided into two categories: more frequent and seasonal allergic conjunctivitis (SAC), and perennial allergic conjunctivitis (PAC), which may also be diagnosed as rhinoconjunctivitis. Perennial allergic conjunctivitis also includes vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis (AKC). Seasonal and perennial allergic conjunctivitis result from exposure of the conjunctiva to an environmental allergen that binds with specific immunoglobulin E (IgE) on the conjunctival mast cells. Examples of common environmental allergens include grass and tree pollens, mites, mould and animal dander.

SAC is classified as an acute allergic reaction and is characterised by peaks of self-limiting signs and symptoms that become persistent with repeated allergen exposure. The main signs and symptoms are itching, redness and lid swelling, but patients may also complain of tearing, mucous discharge and burning. PAC is usually milder than SAC with non-specific signs and symptoms of redness, burning, low level itching and chemosis that persist with varying severity for months, resulting in a chronic condition. Atopic keratoconjunctivitis is the ocular manifestation of a complex and systemic altered immune response, often associated with atopic dermatitis and with other allergic disorders such as rhinitis and asthma.

## Allergic reaction

Mast cells play a key role in the ocular allergic reaction. Studies have shown that during the pollen season the median mast cell numbers in the conjunctiva increased by up to 61 per cent in SAC patients compared to normal subjects, and remained increased in allergic patients out of season.[5] The total number of mast cells is increased in the stroma and epithelium of VKC and AKC patients. Activated mast cells can release several cytokines and other chemicals that have profound effects on the mucosa and contribute to the recruitment of inflammatory cells.

The immediate allergic response lasts clinically for 20 to 30 minutes and induces enhanced tear levels of histamine, tryptase, prostaglandins and leukotrienes. Mast cell degranulation also induces activation of vascular endothelial cells and consequent expression of chemokines and adhesion molecules. These factors initiate the recruitment phase of inflammatory cells in the conjunctival mucosa, the ocular late-phase reaction, which characterises the ocular signs and symptoms in perennial and chronic allergic diseases. In addition, conjunctival and corneal epithelial cells and fibroblasts may contribute to the mounting allergic inflammation by expressing and producing inflammatory chemicals that maintain the local inflammation.

Studies have shown a positive association between eye rubbing and keratoconus. It was found in a case-controlled, multivariate analysis involving 120 patients that eye-rubbing, a form of chronic trauma, is the only significant predictor of keratoconus.[6] Postulated mechanisms on how eye rubbing may precipitate keratoconus include mechanical trauma to the keratocytes, abnormal enzyme activity and a release of inflammatory mediators resulting in a reduction of stromal stability.

Corneal distortion occurs as the force of the intraocular pressure is applied to the weakened cornea. As keratoconus progresses, the cornea thins, thereby increasing the rate of corneal distortion and the potential for poor quality vision. Eye rubbing in response to itching from ocular allergies must be avoided.

Prevention of ocular allergies is achieved by avoiding exposure to the precipitating allergens. One of my patients completely cleared her perennial allergic rhinoconjunctivitis by moving to Moscow in the Winter, which is not always a practical solution. Relieving itching, which is the major symptom of ocular allergy, can be achieved with various topical and oral medications.

# keratoconus patients

The only way keratoconus sufferers should rub their eyes is with their elbows

## Ocular allergy treatment

- **Oral**

Oral antihistamines may be sufficient to control general allergic reactions as well as mild ocular symptoms. Example of oral anti-histamines include Telfast (fexofenadine hydrochloride), Claratyne (loratadine) and Zyrtec (cetirizine hydrochloride).

- **Topical**

Previously, topical antihistamine/vasoconstrictor drops were used to relieve the symptoms of ocular allergy, but it was found that their regular use might lead to rebound dilation of the conjunctival blood vessels. The antihistamine/vasoconstrictor combination drops have been replaced by selective antihistamine drops such as Livostin (levocabastine 0.05%), a highly selective H1-antagonist that is potent and fast acting with a sustained duration of action. The antihistamine blocks the H1-receptors on the nerve endings and vascular endothelial cells, thereby preventing the release of histamine from the mast cells and avoiding the symptoms of redness, chemosis and itching.

Mast cell stabilisers, developed to prevent mast cell degranulation, provide only limited relief from the acute symptoms of SAC due to their lack of antihistamine activity. Examples of mast cell stabilisers include Lomide (lodoxamide trometamol 0.1%) and Opticrom (sodium cromoglycate 2%).

The most effective current treatments are dual-action mast cell stabilisers and antihistamine drops such as Patanol (olopatadine hydrochloride 0.1%) and Zaditen (ketotifen 0.025%). These medications have a rapid onset of action of just a few minutes and have a prolonged duration. Both medications are bid. Patanol requires a prescription and Zaditen is OTC. Zaditen is also available in unit dose vial packs, making it suitable for intermittent use and as an alternative for patients who are allergic to the preservative Benzalkonium Cl used in Patanol and Zaditen bottles.

Most patients will find either option very effective but a small number will have a specific preference for one or the other. If a patient does not report a significant reduction in their symptoms with the first choice or experiences significant side-effects, then I recommend a trial with the other drop. Headaches have been reported in seven per cent of patients using Patanol and stinging, burning and punctate corneal erosions have been reported in one to two per cent of patients using Zaditen. Patanol can be used continually for up to 14 weeks while Zaditen has no restriction on duration of use.

## Clinical advice

Patients who have a family history of keratoconus should be advised to control their allergies, especially their ocular allergies, to prevent itching and consequent eye rubbing. This is especially pertinent for children because the earlier the onset of keratoconus, the greater the likelihood of progression. Despite the availability of collagen cross-linking treatment to strengthen and stabilise the keratoconic cornea, a prevention strategy must be implemented. When I examine children who have allergies and/or a family history of keratoconus, I discuss the issue of allergies and the treatment options. I advise children that the only way they should rub their eyes is with their elbow. I have had numerous dedicated white-knuckled eye-rubbing patients with progressive keratoconus who have never been advised to avoid eye rubbing by their previous practitioners. They are frustrated that they may have been unwittingly contributing to the progression of their condition.

Patients are usually aware of the time of year their allergy sensitivity begins so I recommend they start medication, oral or topical, a month or so before that date, depending on the season, to reduce their symptoms. This applies equally to non-contact lens wearing patients who have early keratoconus and to those with advanced keratoconus or corneal grafts who are wearing RGP lenses.


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# Modern lifestyle

Matt Trollope

**An Access Economics report in 2007 highlighted the emergence of allergy as a major public health problem throughout the 20th Century, identifying Australia and New Zealand as countries with some of the highest rates of allergy in the developed world.**

The report stated that almost 20 per cent of Australians—or more than four million people—suffered from at least one form of allergy, and that there were 7.2 million allergy cases, representing an average of 1.74 comorbid allergies per sufferer. The prevalence of allergy was highest among people aged between 15 and 64 years and represented 78 per cent of all cases.

Allergy can be the cause of asthma, eczema, rhinitis, conjunctivitis and sinusitis, and reactions to certain foods, plants, insects and other substances. Among young Australians, some of the most commonly reported long-term illnesses include asthma, hay fever and chronic sinusitis. Allergic asthma and sinusitis rates have plateaued or decreased, while other allergic conditions such as eczema and rhinitis are rising. Some have demonstrated an alarming increase.

> **With the increasing sanitation associated with a Western lifestyle, people have had reduced microbial exposure, which has led to an increase in both allergic and autoimmune conditions.**
>
> Dr Mimi Tang

The report pointed to the rapid rise of food allergy and anaphylaxis in Australia, with food anaphylaxis hospitalisations doubling in the past decade and increasing five-fold among children aged between birth and four years of age. Peanut allergies have doubled in prevalence among young children over the past five years.

Dr Raymond Mullins, a Canberra-based clinical immunologist and allergy physician, conducted a study analysing rates of food allergy and anaphylaxis. He reviewed data for children up to five years old who had been referred to a specialist immunology and allergy clinic in the Australian Capital Territory between 1995 and 2006, and reported a 12-fold increase in the number of children diagnosed with food allergy over this period. Rates of food anaphylaxis diagnosis increased more than seven-fold.

'There is an urgent need for co-ordinated systematic studies of the epidemiology of food allergy in Australia, to ascertain risk factors and guide public health policy,' he says.

The rise in allergy has not been restricted to children. Dr Mimi Tang, a paediatric allergist immunologist at Melbourne's Royal Children's Hospital, says a recent analysis of anaphylaxis hospital admissions revealed that for non-food anaphylaxis, admission rates had increased among those aged 55 years and over and was predominantly related to drug allergy.

## Why the rise?

The reason for the recent rise in allergy prevalence in Australia is unknown. With several theories proposed, ultimately a combination of factors could explain this trend.

Increases in pollution, the use of non-steroidal anti-inflammatory drugs, and the consumption of processed and refined foods containing unrecognised allergens are several hypotheses for the rise in allergies. Others include vaccinations, non-exclusive breastfeeding, food preparation techniques, and the stage at which certain foods are introduced to children.

The most popular explanation is the 'hygiene

Rebuilding our depleted immune system may be the best defence in the fight against the increase in the prevalence of allergy

# fuels epidemic

hypothesis' or 'microbial hypothesis'. Tang says the rise in allergy has occurred predominantly in the developed countries of the Western world. 'It is believed that we need early and broad exposure to a wide range of microbial stimuli in early life, including in the womb, to appropriately train our developing immune systems not to overreact to common environmental allergens or self antigens and to respond only when there is a real threat,' she says.

'With the increasing sanitation associated with a Western lifestyle, people have had reduced microbial exposure, which has led to an increase in both allergic and autoimmune conditions such as coeliac disease and type 1 diabetes. This is due to the immune system mounting unwanted responses to either environmental allergens like pollen or food proteins, or self antigens in the case of autoimmune disease.

'We don't wish to return to the less sanitary conditions of previous eras and risk the increase of cholera, salmonella or typhoid, but we have probably gone too far with the sanitation and sterilisation of our environment through antibacterial sprays and sterilisation of foods.'

While much of the literature on allergy prevalence has focused on the rising rates of food allergy in children, an increase in drug-related allergy has been reported in adults and people aged over 55 years.

Tang says she has also noticed a rise in the incidence of ocular allergy, which she says is commonly associated with allergic rhinitis.

## Implications

Allergies significantly impact on a person's quality of life. In children, allergies can affect sleep and impair learning, memory and behaviour. For children with more severe conditions such as food allergy and anaphylaxis, not only do they suffer, but their families endure high levels of stress worrying about issues such as their child's welfare at school, access to emergency medication and higher risk of death.

Children are not the only age group affected. The Access Economics report said that in 2007, the financial cost of allergies was $7.8 billion, with the majority of that sum representing productivity lost due to lower productivity at work, less employment, absenteeism and premature death. Other allergy-related costs included direct health system expenditure and money spent on welfare payments, aids and home modifications. In the report it was said that the net value of lost well-being—relating to disability and premature death—was an additional $21.6 billion, almost double the equivalent net value for both arthritis and hearing loss.

If the incidence of allergy continues to rise at its current rate, according to the report there would be 7.7 million Australians suffering with at least one allergy by 2050, a 70 per cent increase in prevalence. Australia world required 178 allergy and immunology specialists by 2017 to cope with the growing demand for these services and to correct the current maldistribution of these practitioners. Current trends indicate that there will be just 115 specialists available by this date.

In the report it was stated: 'In Australia there is a lack of public and professional appreciation of the impact of allergic and immune disorders on quality of life, and even less of the economic impact to society and individuals who suffer allergic disease.'

Tang says that the burden of allergic disease on both sufferers and Australia's health system is compounded by the fact that allergies are chronic diseases with no cure. 'We need to work towards prevention strategies but also need to develop treatment strategies to address the very significant burden of disease that already exists. To do this we must understand the factors that lead to allergic disease and try to target modifiable factors.' she says.

'Research into prevention is focused on understanding and identifying environmental risk factors for developing allergy as these factors are likely to be modifiable. Research into treatment strategies are focused on understanding the immune mechanisms involved in allergy, and also the mechanisms operating in those who have spontaneously grown out of their disease in order to identify specific immune parameters that could be manipulated to resolve a person's allergy.'

## Case report

# Tapering Lucentis treatment raises alarm

**Dr Suzanne Cochrane**
MBBS(Hons) FRANZCO

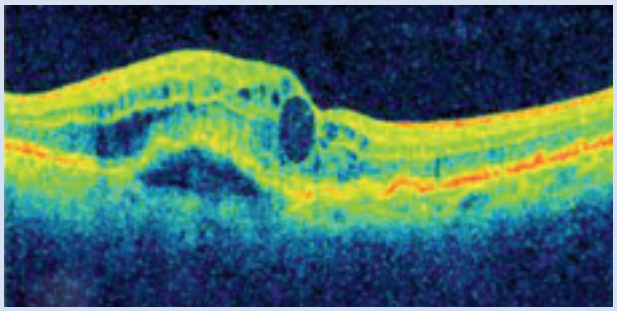

**Figure 1. Spectralis OCT of right fovea at presentation (visual acuity 6/15, N12) showing a pigment epithelial detachment and intraretinal cystic oedema**

An 89-year-old woman presented with bilateral simultaneous visual deterioration, secondary to occult choroidal neovascularisation. Her visual acuities were right 6/15, left 6/24, N12, and she was struggling to cope at home. Three months earlier her visual acuities were recorded as 6/9, N6 bilaterally, with mild dry AMD. Ongoing monthly Lucentis treatment has maintained her vision at right 6/9, left 6/12, N6. Less frequent treatment was associated with recurrence of her subfoveal leak and visual deterioration, so she continues to present for treatment every two weeks.

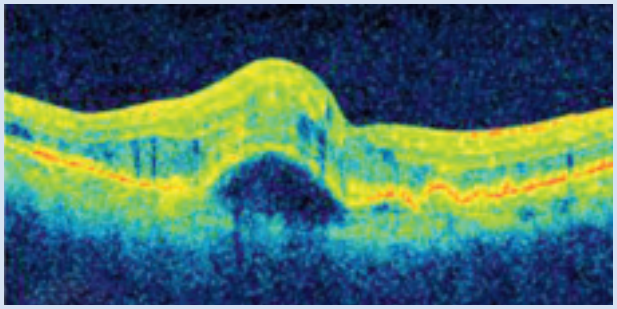

**Figure 2. Spectral-domain OCT of the left fovea at presentation (visual acuity 6/24, N12) showing a pigment epithelial detachment and intraretinal cystic oedema**

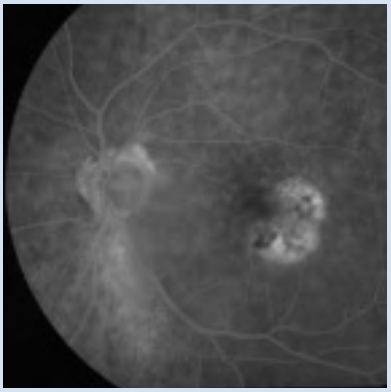

**Figure 3. Fundus fluorescein angiogram of the right eye at presentation (late phase) demonstrating occult choroidal neovascularisation**

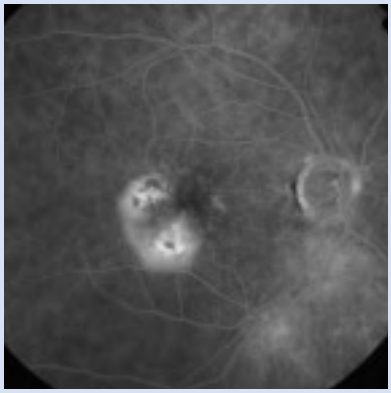

**Figure 4. Fundus fluorescein angiogram of the left eye at presentation (late phase) demonstrating occult choroidal neovascularisation**

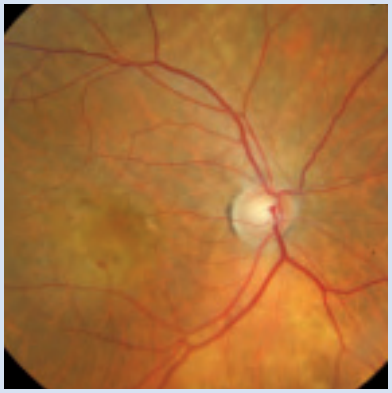

**Figure 5. Colour fundus photograph of the right eye at presentation demonstrating subretinal haemorrhage, a pigment epithelial detachment in addition to her pre-existing soft drusen and pigment epithelial change**

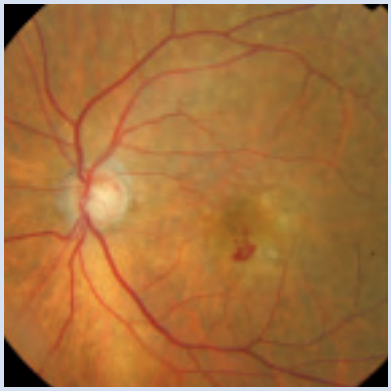

**Figure 6. Colour fundus photograph of the left eye at presentation demonstrating a clinical picture similar to that of the right eye**

# Progress in AMD

New studies offer hope of not only slowing AMD progression but also preventing the disease

**Jennifer Keller** BS
**Leonid Skorin Jr**
DO OD FAAO FAOCO

**Age-related macular degeneration (AMD) is the leading cause of blindness in the developed world for people over 50 years of age.[1] It is a multifactorial disease that involves the relationship of age, familial inheritance, diet and environmental factors such as smoking, obesity and hypertension. AMD can reduce or eliminate a person's ability to participate in daily activities, resulting in loss of independence and possible depression.**

We know that degenerative damage of AMD results from oxidative stress and deposition of metabolic end products in the macular region but because the exact mechanism of AMD is still a mystery, finding a cure is difficult. Thankfully, studies like the Age-Related Eye Disease Study (AREDS) have provided us with some hope of decreasing the risk of AMD progression. Since the release of AREDS, numerous studies have followed, aimed at the prevention of AMD.

## AREDS

From the Age-Related Eye Disease Study a high-dose antioxidant supplement was developed containing vitamin C, vitamin E, beta-carotene and zinc. The study determined that individuals with intermediate AMD or advanced AMD in one eye had a 25 per cent reduced risk of progressing to advanced AMD compared to individuals taking a placebo.[2]

The good news is that AREDS gives us armor for high-risk AMD patients. The bad news is that there is no solid treatment on the horizon for early AMD patients. Beta-carotene has been shown to increase the risk of lung cancer so AREDS is not a viable option for AMD patients who smoke.[2] The AREDS study was conducted for only 6.3 years. The safety of taking the AREDS formula for longer periods has not been tested.

The Age-Related Eye Disease Study 2 (AREDS2) is underway to determine how dietary supplements high in lutein, zeaxanthin and omega-3 long chain polyunsaturated fatty acids affect the development of advanced AMD. It is also looking at a modification of the original AREDS formula. AREDS2 eliminates beta-carotene while lowering the amounts of zinc.[3] AREDS2 finished enrolment in 2008 and will be following participants of the study for five to six years.

## Vitamin E

AREDS shows some benefit to high-risk patients but, even after multiple studies in this area, the exact beneficial component is still unknown. Recent evidence demonstrates supplementation of vitamin E (a component of AREDS) has no effect on reducing the risk of developing advanced AMD.[4] As the largest trial of vitamin E supplementation in AMD to date, the findings are hard to dispute. The findings do acknowledge that although vitamin E alone shows no benefit, when combined with other antioxidants there could be some potential benefit.

## Omega-3s

The Western diet is the root of many of society's diseases including obesity, diabetes and AMD. Everywhere you look you will find confirmation of omega-3s improving our health. Omega-3 fatty acids (docosahexaenoic acid [DHA] and eicosapentaenoic acid [EPA]) have been shown to be protective against progression to advanced AMD.[5] Two to three servings each week of cold-water fatty fish such as salmon, tuna, mackerel, shellfish and herring are sufficient to reach recommended DHA and EPA levels. This study also found that patients can reduce the risk of progressive AMD by decreasing their dietary glycaemic index. This can be done by replacing refined carbohydrates (white bread and flour) with whole grain products. The risk of ARMD progression is further reduced when these two strategies are combined. This study claims that if started at the earliest stages of AMD, this method may be the most protective means against progression of early AMD.

## Smoking

Age is the strongest risk factor for AMD, followed closely by cigarette smoking. Age is an inevitable risk factor, compared to smoking which is a controllable variable. Smoking is thought to increase risk of AMD by reducing serum antioxidant levels, altering choroidal blood flow and decreasing luteal pigments.[6] A recent study has observed how age (older than 80 years) and smoking affect one's risk of AMD. The evidence indicates smokers older than 80 years are at a significantly higher risk of developing early AMD compared to non-smokers of the same age.[6] This study suggests yet another reason why smoking can be detrimental to your health.

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# Tailor therapy corneal

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**Corneal ulceration or ulcerative keratitis is a disruption of epithelium with underlying stromal loss or inflammation.[1] A persistent epithelial defect following delayed epithelial closure[2] exposes the underlying stroma to the environment, allowing damage to ensue. This may occur as a result of tear film anomalies, toxic reactions or metabolic disorders, trauma, microbial or chemical insult, contact lenses or surgery.**

In the absence of healing, persistent epithelial defect progresses towards basement membrane disruption. Even in the face of constant environmental assault, corneal ulcers are relatively rare. The annualised incidence in a recent Australian study of soft contact lens-related microbial keratitis ranged from 1.1 to 1.15 per 10,000 wearers.[3]

Ulcers develop in response to persistent epithelial damage. Ulcers can be sterile or infectious. Fini and colleagues have described ulceration as arising from pathological wound healing and characterised by gelatinisation of the corneal stroma, often referred to as corneal 'melting'.[4]

Infective ulcers (ulcerative keratitis or microbial keratitis) can be of bacterial, viral, fungal or protozoal origin. The most common form of infectious corneal ulcer is bacterial.[1] Contact lens wear is frequently associated with severe microbial keratits.[5] *Staphylococcus* species continue to be the predominant cause of bacterial keratitis.[6] In the southern part of the United States, *Pseudomonas* is reported as the most commonly isolated organism, especially in association with daily or extended wear soft contact lenses.[7] Corneal trauma, previous ocular surgery, ocular surface disease, systemic illness and secondary infection arising from abuse of topical ophthalmologic drugs are all associated with high rates of infectious corneal ulceration.[8] Contact lens wear has been reported in up to 56 per cent of cases.[9] Ocular chemical injuries account for seven to 18 per cent of ocular trauma in the United States.[10]

Treatment needs to be co-ordinated and immediate and tailored to the aetiology of the ulcer as sterile or infectious. Various agents have been tested in treatment of ulceration including growth factors, anti-inflammatories and immune-response modulators. This review highlights recent advances in our understanding of the corneal ulceration wound healing therapeutics.

Since most conditions that lead to ulceration involve substantial inflammation and associated secretion of proteases such as matrix metalloproteinases (MMPs) it was hypothesised that treatment with MMP inhibitors would reduce the severity of ulceration. Tetracycline, doxycline and monocyline all weakly inhibit MMPs and were tested in treatment of chemical corneal injury. Initial results were encouraging but no large multi-centre studies have been conducted to rigorously assess these agents.[1] Ilomastat, a small synthetic inhibitor of MMPs, showed great promise in a large clinical trial[11] but has not been brought to market. IL-1β has been shown to be involved in up-regulation of MMPs in corneal epithelial cell culture.[12] Inhibition of IL-1β through anti-IL-1β antibody administration caused a concomitant reduction in MMP-9 during infection and reduced corneal damage,[13] thus highlighting a potential novel therapeutic strategy for the treatment of bacterial keratitis.

Corticosteroids play an ambiguous role in treatment of corneal ulceration, with topical steroids reported variously as ameliorating[14] or exacerbating chemical ulceration.[15] Topical steroids decrease inflammation by inhibiting production of arachadonic acid and IL-1,[1] which ultimately decreases production of MMPs, but steroids also decrease the rate of wound healing. Understanding the mechanism of action of steroids is essential for beneficial use in ulceration. Steroids should be used when ulceration is secondary to inflammation but can be deleterious when there is no inflammation.

Expression of interleukins Il-1β and IL-6, among others, are induced after alkali burn leading to a cascade of epithelial wound healing events.[10] Exogenous application of IL-6 has been shown to promote corneal wound healing[16] and to reduce bacterial corneal infection through recruitment of neutrophils.[17] IL-10 appears relatively late in the immune response and regulates expression of IL-6. Investigations into the actions of IL-10 have highlighted in bacterial keratitis models the delicate balance between inflammation and angiogenesis.

Mice lacking IL-10 cleared bacterial load challenge and reduced inflammation but suffered concomitant deleterious angiogenesis of the cornea.[18] Treatment with a novel angiogenesis inhibitor 12-MTA in both alkali injury and *Pseudomonas aeruginosa* infection models showed significant advantages over current treatments such as dexamethasone in reducing incursion of new blood vessels into the central cornea along with reduction of penetration of PMN infiltration.[19]

Various exogenous growth factors and cytokines have been used in the treatment of corneal epithelial wounds.[20] Numerous reports have indicated topical administration of acidic and basic growth factors in accelerating healing of epithelial scrape injury in rabbits,[21,22] while recombinant human epidermal growth factor has shown great promise in randomised clinical trials of acute traumatic epithelial abrasions or corneal ulcers but not in mechanically induced defects following penetrating keratoplasty.[23-25]

Nerve growth has been shown to pro-

# to suit wound

mote healing in corneal and skin ulcers potentially through stimulation of new nerve fibres and collagen production by fibroblasts and, with the availability of human recombinant NGF, holds promise as a novel therapeutic strategy.[26]

Lactoferrin, a glycoprotein present in various bodily secretions, has been shown to reduce inflammation, modulate the immune response and counter bacterial infection.[27] Pattamatta and colleagues[10] have demonstrated *in vitro* and *in vivo* stimulation of corneal epithelial cell wound healing with application of bovine lactoferrin, thereby suggesting potential clinical applications for therapeutic intervention.

Finally, carboxymethylcellulose (CMC) has been shown to be efficacious in the treatment of aqueous tear-deficient dry eye symptoms[28] and is used as an additive in artificial tears applied following laser *in situ* keratomileusis to aid post-operative ocular surface recovery.[29] CMC also demonstrates beneficial effects on the ocular surface when used prior to contact lens insertion.[30] Tear film lubrication helps protect against ulcerations through reduction of corneal erosion and removal of ocular pathogens. Garrett and colleagues have shown efficacy of CMC in promotion of corneal epithelial wound healing *in vitro*[31] (Figure1) and in a rabbit corneal epithelial scrape wound model[32] through the formation of epithelial tight junctions in the restoration of corneal epithelial integrity (Figure 2).

The corneal epithelium, though thin and transparent, is a robust first defence against daily environmental assault. Persistent epithelial defects are necessary to induce corneal ulceration. These defects may arise from chemical, microbial or immune-mediated agents. Care must be taken to correctly assess the aetiology of ulceration as inappropriate treatments such as anti-inflammatories can exacerbate rather than ameliorate the condition by lowering immunity. Conversely, toxic antimicrobial therapy in the treatment of non-infectious ulcers can be deleterious.

Therapy must be tailored based on patient history and physical examination. Promising new therapeutics are being investigated that may offer more specific targeting, greater efficacy and result in fewer adverse side-effects.


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# High stakes: periphe

It's a gamble but you can shorten the odds if you know when to draw, when to hold and when to fold.

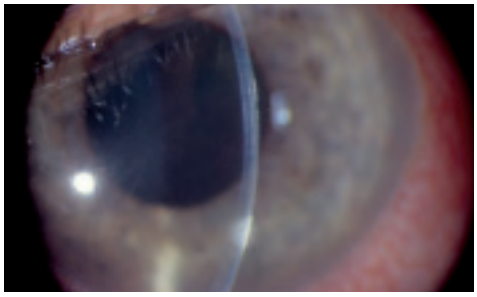


Figure 1. Dense circular infiltrate inferiorly with a fine lamellar layer of cells in stroma seen extending above the infiltrate

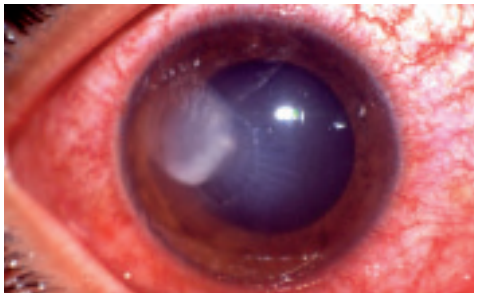


Figure 2A. Larger dense infiltrate with stroma edema extending centrally with striae and an obvious overlying epithelial defect

**When a patient walks into your consulting room with corneal infiltrate, it is like you are about to sit down to a hand of poker. The outcome is unknown and your actions are determined by working the odds—hopefully in the patient's favour.**

You need to know when to draw cards (treat the patient), when to hold the cards you have (just observe the patient), and when to fold (refer the patient). Unlike playing poker, when treating a patient with corneal infiltrate there is much more than money at stake, so it is important that you take the right course of action.

## The poker game

Is the corneal change you are seeing in the slitlamp a corneal infiltrate? It is usually a relatively dense white accumulation of stromal material that, seen at high magnification though a slitlamp, comprises minute white spots with the surrounding stroma also peppered with fine white spots decreasing in number the further the slitlamp beam moves away from the central dense spot (Figure 1).

The condition is different from a corneal nebula (scar) or corneal lipid deposit. A corneal scar is usually uniformly white, restricted to a defined lamella of the cornea with no corneal cellular activity and a quiet eye (Figures 2A and 2B). An eye with recurrent disease such as marginal keratitis may have both nebulae or scars from previous attacks as well as an acute infiltrate from the current episode (Figures 3A, 3B and 3C). Corneal lipid deposit is usually but not always almost crystalline in appearance and observed in the background of a quiet eye, and frequently with associated vascularisation of the stroma (Figure 4).

## Ready to start playing?

There are many brands of poker. Before you can be dealt a hand, you need to know the rules of the game. Likewise, understanding the definition of various degrees or types of corneal infiltrates is important.

- **Corneal infiltrate**: corneal stromal opacity usually with evidence of some surrounding stromal scattering of cells with or without a small overlying epithelial defect and with or without anterior chamber activity (Figure 1).
- **Corneal ulcer**: corneal infiltrate with overlying epithelial defect and frequently some loss of stromal substance with anterior chamber activity (Figure 5).
- **Corneal abscess**: dense stromal opacity with surrounding stromal cellular activity, oedema and almost always associated

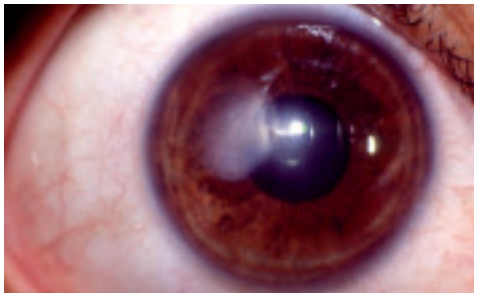


Figure 2B. Same eye after only two weeks of treatment showing characteristic early scar (nebula) formation; compare to 2A

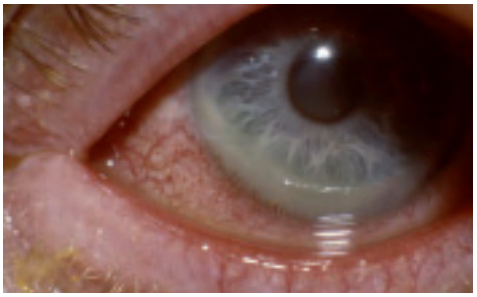


Figure 3A. Severe but typical peripheral, perilimbal infiltrate with localised ciliary injection seen in marginal keratitis

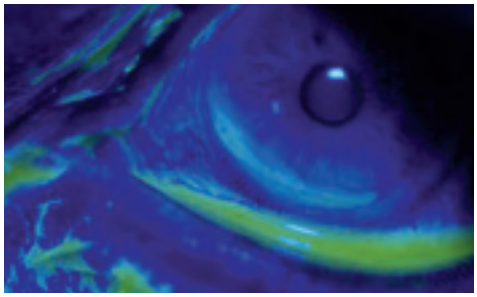


Figure 3B. Fluorescein staining shows a circumferential epithelial defect

# ral corneal ulcers

**Dr Lawrence Hirst**
MBBS DO FRANZCO
FRACS MD MPH

with severe anterior chamber activity or hypopyon (Figure 6).

- **Corneal abrasion**: corneal epithelial defect usually as a result of trauma such as a scratch or trichiasis (Figure 7).
- **Corneal epithelial defect**: corneal epithelial defect without any underlying stromal opacity and no history of trauma (Figure 8).

We cover only the first type of a corneal infiltrate. We are discussing patients with a corneal opacity as a result of cellular infiltration and perhaps a small epithelial defect with slight anterior chamber reaction in some cases. Once there is stromal thinning, the condition enters the much more concerning phase of a corneal ulcer. A corneal abscess is a devastating corneal condition that may quickly lead to perforation. I reserve the term corneal abrasion and epithelial defect for where there is no corneal infiltrate.

## Evaluate the other players at the table

To win at poker you need to be able to read the other players, their characteristics, speech and physical habits, especially when determining whether they are bluffing. Likewise, by taking the patient history and the slitlamp evaluation of the infiltrate, you can better understand the type of infiltrate with which you are dealing, relatively innocent or potentially devastating.

**History**

- trauma
- contact lens: specifications
- eye-drops
- surgery
- other similar episodes
- speed of progression

**Symptoms**

- pain
- light sensitivity
- vision

**Examination**

- position (Figures 1, 2A, 3A, 5)
- number (Figures 1, 9)
- size (Figures 1, 2A, 5)
- depth (Figures 10A, 10B)
- thinning (Figures 11A, 11B)
- morphology (Figures 1, 2A, 6)
- bilaterality
- scars (Figure 12)
- epithelial defect
- vascularisation (Figure 13)
- anterior chamber activity (Figure 14)
- injection: conjunctival (Figure 15), ciliary (Figure 16)

**Continued page 20**

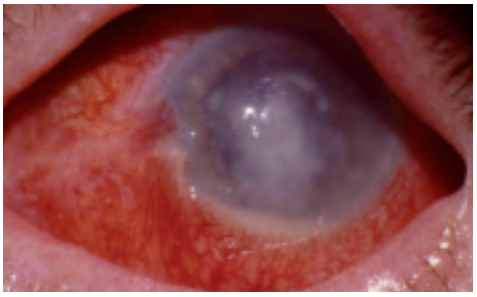


**Figure 5. A fungal corneal ulcer consisting of a large central corneal infiltrate with surrounding satellite lesions and hypopyon**

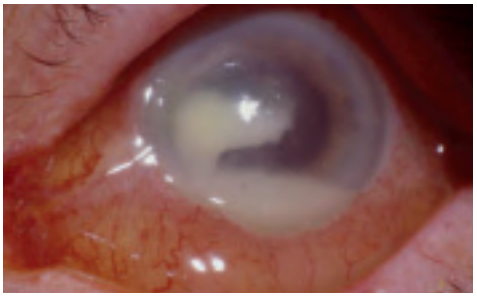


**Figure 6. A fungal corneal abscess with a uniformly dense corneal opacity and large hypopyon**

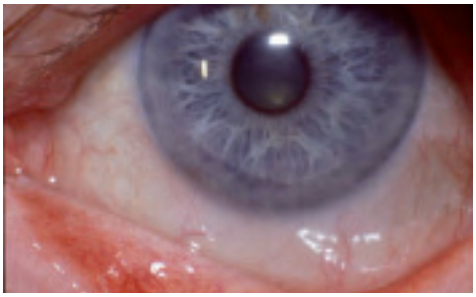


**Figure 3C. Same eye after one week of topical steroid use**

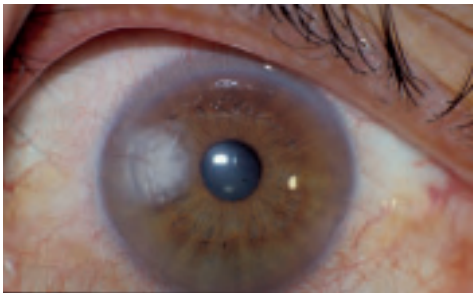


**Figure 4. Note a central stromal blood vessel surrounded by a dense lipid deposit in a quiet eye**

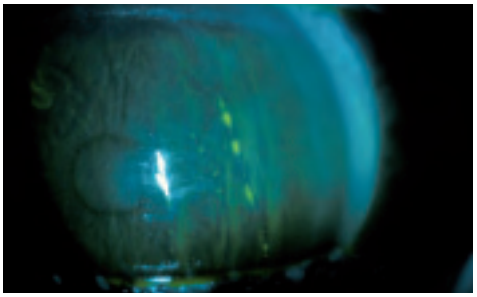


**Figure 7. Fluorescein staining of a linear corneal scratch**

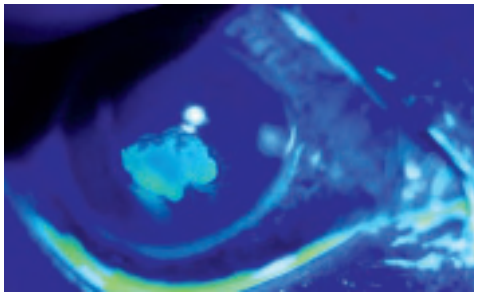


**Figure 8. Irregular corneal epithelial defect by fluorescein staining**

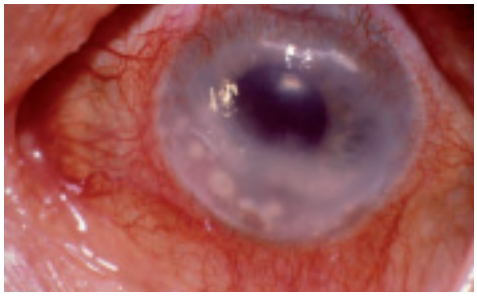


**Figure 9. Cornea showing five or six discrete corneal infiltrates infero-nasally and two other infiltrates, paracentrally and superiorly; this eye also demonstrates corneal neovascularisation above and has gross ciliary injection**

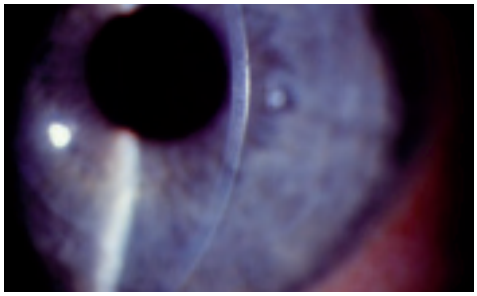


**Figure 10A. The infiltrate seen in the center of the slit beam is very superficial**

**Tests**

- Subtarsal examination (Figures 17A, 17B, 17C)
- lid examination, lashes, meibomian glands
- corneal sensation
- fluorescein staining
- IOP
- vision

Using the table (right) you can approximate the severity of the situation. If you answer eight or more for any of the above categories of history, symptoms, examinations or tests, then you should refer the patient to a specialist. Otherwise, proceed with caution.

## Are you ready to bet?

You will need to know whether to draw some cards and treat the patient, hold the cards you have and observe the patient, or fold your hand and refer the patient to an ophthalmologist. The flow chart (page 22) is a starting point to guide your decision-making process. If along the way the patient's condition becomes an unwinnable hand, your strategy may have to change.

## How much should you bet?

### Steroids

If you have a great hand then put all your money on this bet; the choice of steroids is much the same and always contentious. If you are certain that the infiltrate is sterile or immunological and the patient is very symptomatic, use prednisolone acetate 1% at least four times a day and up to every two hours while awake. Although this can give you the quickest result (Figures 2A and 2B), you can also lose the game if you are wrong (Figures 20A and 20B).

If you have a modest hand, you may want

| History | Grading of severity<br>10 urgent to 1 non-urgent |
|---|---|
| Surgery especially refractive, PK | 10 |
| Rapid onset and progression (over 1-2 days) | 10 |
| Trauma especially vegetable | 7 |
| Contact lens wear | 7 |
| Chronic use of drops especially steroids, or antibiotics | 10 |
| Other previous similar attacks | 5 |
| None of the above | 5 |
| **Symptoms** | |
| Severe unremitting pain | 10 |
| Reduced vision | 10 |
| Light sensitivity | 5 |
| **Examination** | |
| Position: peripheral | 5 |
| Position: non-peripheral | 7 |
| Size: less than 1 mm | 5 |
| Size: 1-2 mm | 7 |
| Size: >2 mm | 10 |
| Depth: just under epithelium and thin | 5 |
| Depth: superficial extending to mid-stroma | 7 |
| Depth: full thickness | 10 |
| Thinning: none | 5 |
| Thinning: slight | 8 |
| Thinning: severe | 9 |
| Thinning: perforation | 10 |
| Number: one | 7 |
| Number: >1 | 3 |
| Morphology: discrete circular | 3 |
| Morphology: irregular | 7 |
| Morphology: feathery (Figure 18) | 10 |
| Morphology:perineural (Figures 16,19) | 10 |
| Epithelial defect: none | 5 |
| Epithelial defect: present | 7 |
| Bilaterality: no | 7 |
| Bilaterality: yes | 5 |
| Vascularisation: yes | 5 |
| Vascularisation: no | 7 |
| Other scars: yes | 5 |
| Other scars: no | 7 |
| Injection: none | 3 |
| Injection: conjunctival only | 5 |
| Injection: ciliary | 7 |
| AC activity: none | 3 |
| AC activity: slight (occasional cell) | 5 |
| AC activity: severe (hypopyon) | 10 |
| **Tests** | |
| Subtarsal: normal | 5 |
| Subtarsal: foreign body | 10 |
| Corneal sensation: intact | 5 |
| Corneal sensation: absent | 10 |
| IOP: normal | 5 |
| IOP: raised | 10 |
| Vision: normal | 5 |
| Vision: reduced | 10 |

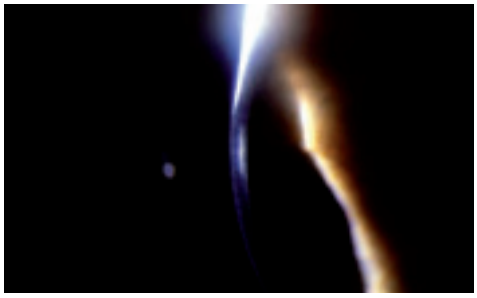


**Figure 10B. The infiltrate here is very deep in the stroma, almost on Descemet's membrane**

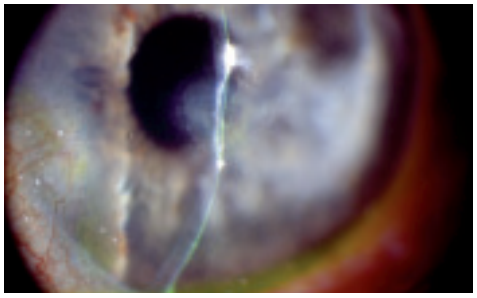


**Figure 11A. Central healing ulcer that shows about 30 to 40 per cent loss of stroma**

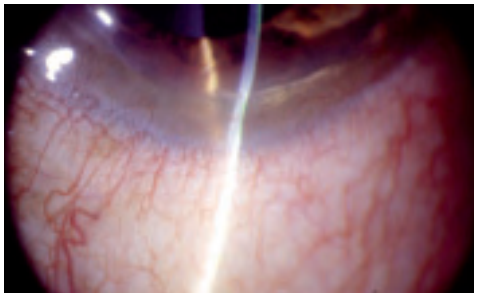


**Figure 11B. The peripheral thinning here is probably no more than 10 per cent loss of stroma**

to add to the kitty and use a mild steroid such as fluorometholone. There is less chance of losing but don't expect the same returns; the condition will take longer to resolve.

**Antibiotics**

You may want to cover your bets and use a broad spectrum antibiotic as very few of these infiltrates are pathognomic and indicate the microbe that is to blame. Second generation fluoroquinolones such as ciprofloxacin are safe bets but will not cover absolutely all gram positive and negative bacteria. Ofloxacin is also useful. Using third and fourth generation fluoroquinolones, which are not available in Australia, you are likely to have a better chance of winning. The antibiotics should be used frequently: about every two hours while awake. Although only ciprofloxacin is currently available in Australia, hopefully others will come.

In aggressive corneal ulcers, fortified antibiotics are frequently prescribed. These are usually formulated by a hospital pharmacy, the most common being fortified gentamicin 15 mg/ml and fortified vancomycin 50 mg/ml. Both may need to be used in a fulminant corneal ulcer where the organism is not identified. These are almost never used for small corneal infiltrates.

**Combination steroids and antibiotics**

If you do not know whether your poker hand is any good you may want to hedge your bets. This is not a good idea because at some time you will have to make a decision. It is recommended that you prescribe antibiotics if you deem the condition infective, otherwise use steroids or patient observation.

## Don't loose your pants

- Corneal infiltrates need daily observation until you are clear about what is going on. Do not even commence treatment of the patient unless you are prepared for this frequent observation–even on weekends.
- If it looks atypical, it probably is and needs to be referred. Don't be brave with the patient's eye.
- Treat the patient only with steroids, antibiotics or observation if the patient is compliant. If you have any doubts about this, refer the patient on to become 'someone else's headache'.
- Any deterioration requires immediate re-evaluation and referral.

Remember the most important rule: know when to hold and when to fold.

**Continued page 22**

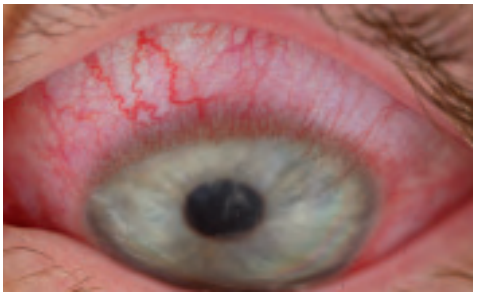


**Figure 16. Principally ciliary injection concentrated around the limbus; note some fine perineural infiltrates in the superior cornea almost pathognomic for acanthamoeba**

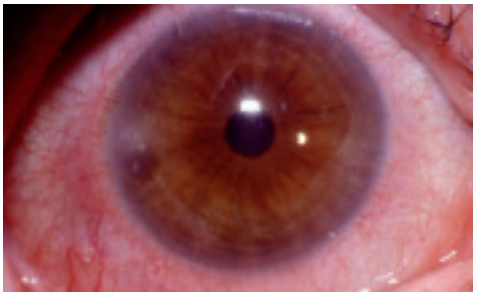


**Figure 17A. A peripheral corneal infiltrate at the 9 o'clock position in the right eye**

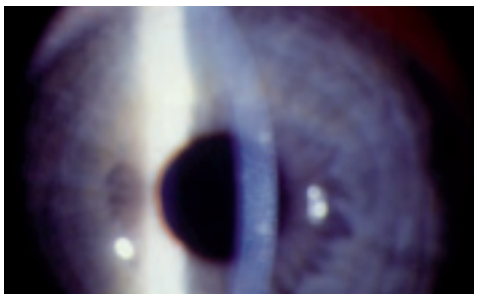


**Figure 12. There are nummular scars present in the central cornea following EKC**

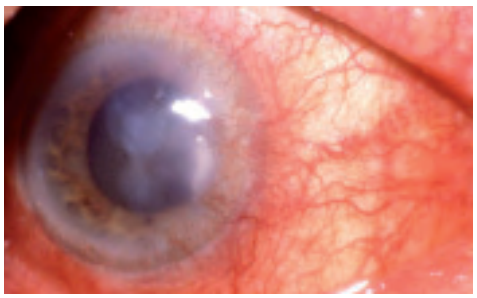


**Figure 13. Dense vascularisation is seen nasally two to three millimetres into the cornea; at the leading edge 3 o'clock position is a linear infiltrate and centrally a corneal scar**

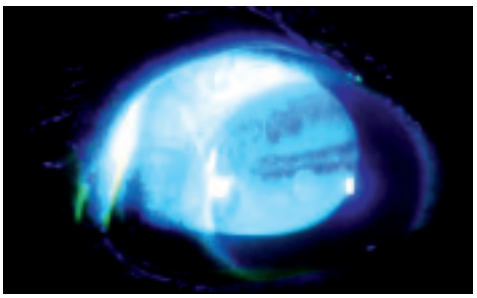


**Figure 17B. Fluorescein staining reveals tell-tale linear scratches in the supero-temporal cornea**

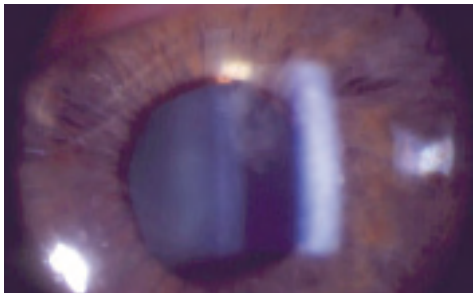


**Figure 14. Flare and cells in anterior chamber**

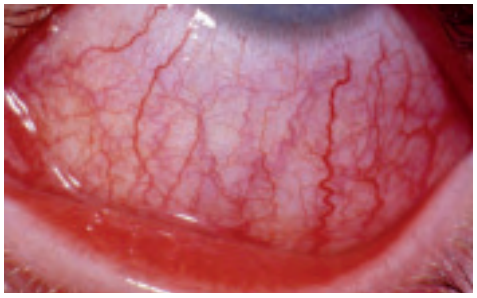


**Figure 15. Note intense conjunctival injection with maximum injection in the fornix**

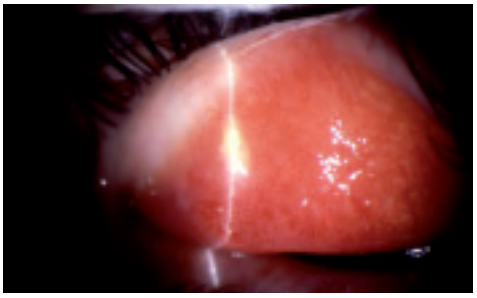


**Figure 17C. The culprit: a subtarsal foreign body, which was an insect wing**

# Peripheral corneal ulcers

**From page 21**

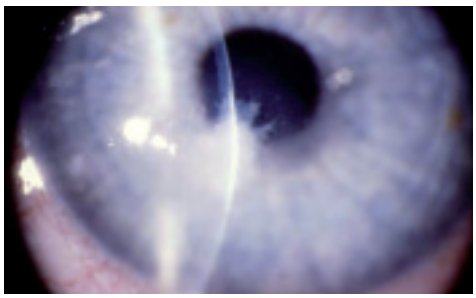


**Figure 18. A dense infiltrate with feathery extensions typical of a fungal infection**

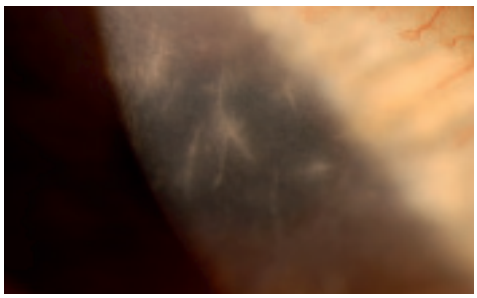


**Figure 19. A high magnification view of same eye as in Figure 16, illustrating the typical infiltration of cells around a bifurcating corneal nerve, seen in early acanthamoeba infections**

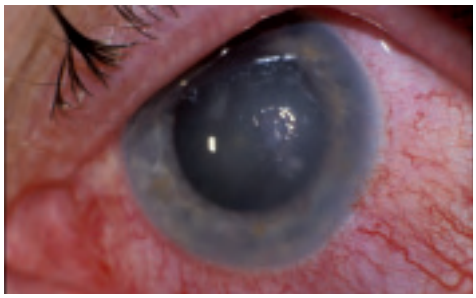


**Figure 20A. Very injected eye with a small temporal infiltrate and overlying epithelial defect**

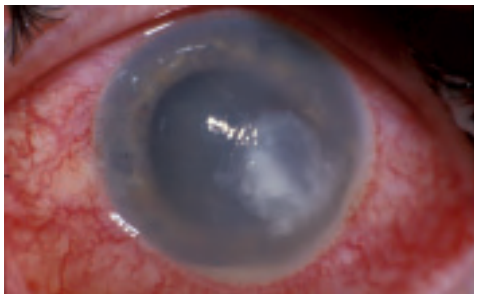
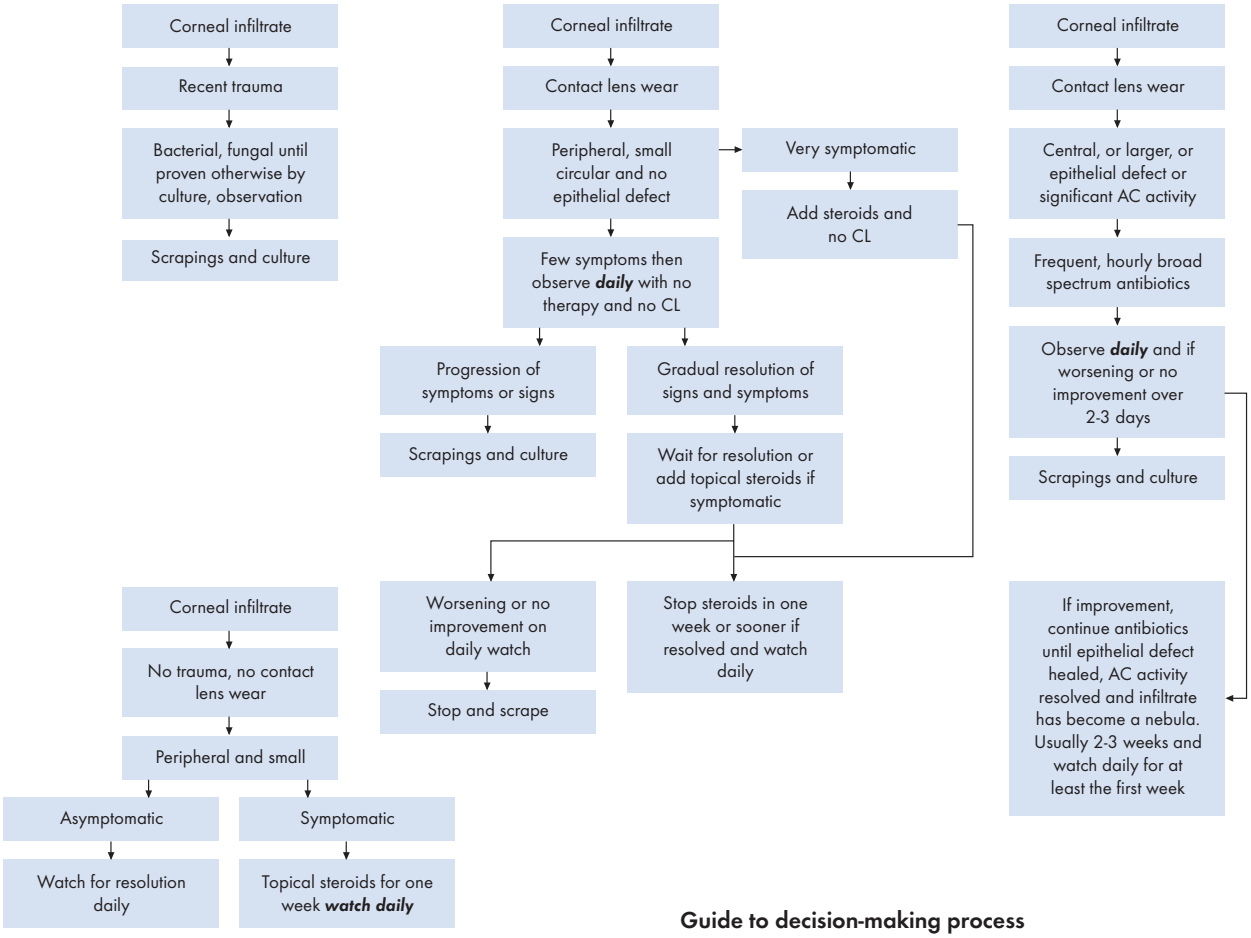


**Figure 20B. After two days of steroid treatment, the infiltrate has increased 10-fold and there is a hypopyon**




**Guide to decision-making process**

Anna Morse takes more accessible primary eye care to remote communities across the Northern Territory. **Jennifer Greive** reports

# Lots to do in outreach

**The most satisfying part of Anna Morse's job is being able to see the benefit her work brings to the community.**

Since becoming therapeutically endorsed two years ago, Morse feels more equipped to provide primary eye care to her patients and says her confidence and accuracy in diagnosing anterior eye diseases has improved.

'Being able to simply prescribe chloramphenicol for a child's bacterial conjunctivitis, or manage a case of recalcitrant allergic conjunctivitis with a short course of FML enhances my clinical scope and job satisfaction,' she said. 'More importantly, it provides a more accessible primary eye-care service to the community.'

Morse is project development officer for the International Centre for Eyecare Education (ICEE) Aboriginal Eye Care Program, and spends half her time providing outreach optometric services to remote Aboriginal communities. She helps teach local health workers the basics of eye care to help strengthen referral pathways.

The rest of Morse's time is spent at Danila Dilba Health Services, Darwin's Aboriginal medical service, where she provides regular consultations and works alongside general practitioners, Aboriginal health workers, nurses, dietitians and other allied and specialist health professionals.

By working with local GPs and pharmacists, she feels she is helping to provide the local Aboriginal community with accessible eye care. 'GPs or health workers often ask me about a patient they are managing, either referring them to me or asking me to pop in to check a red eye,' she said. 'I have also established a good relationship with the Royal Darwin Hospital ophthalmology clinic.'

Optometrists in the Northern Territory can prescribe ocular therapeutic medicines including anti-glaucoma preparations but patient follow-up can be difficult, especially in remote areas where an optometrist may visit only once or twice a year.

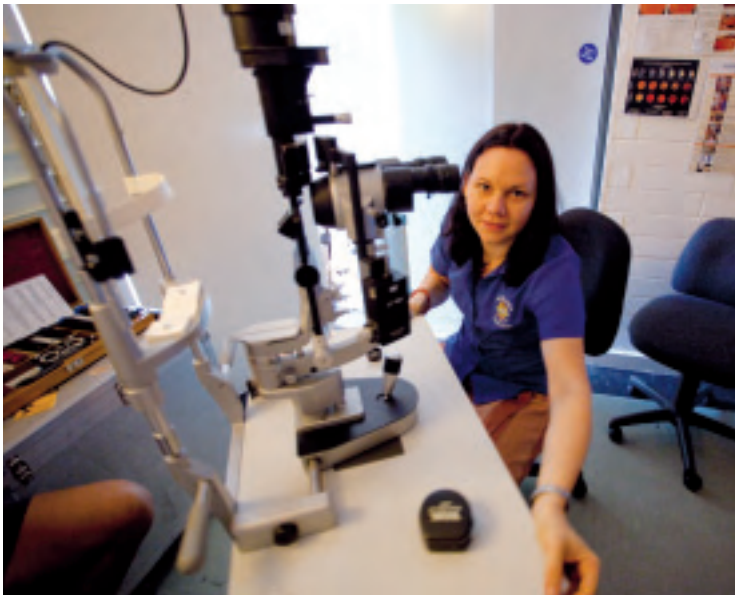


Photo: Dean Saffron, ICEE

The most commonly prescribed topical ocular drugs are always available at Danila Dilba, and some remote clinics stock prednisolone or dexamethasone for patients who have undergone cataract surgery.

Some remote clinics stock prednisolone or dexamethasone for patients who have undergone cataract surgery.

'Cataracts are very common, particularly in remote communities in the Northern Territory where blinding cataracts are not unusual,' Morse said. 'This may be caused by the accumulated UV exposure that comes with living in the Territory. There is a misperception among some people that loss of vision and even blindness is just a normal part of ageing. Some fear cataract surgery, believing that people who go to hospital often don't return.'

Prior to joining ICEE, Morse practised at Laubman & Pank in Alice Springs for four years, participating in regular outreach eye clinics with an ophthalmologist and providing locum service across Australia.

She worked as a locum in Brisbane while studying therapeutics at Queensland University of Technology, having secured a scholarship from Services for Australian Rural and Remote Allied Health, which covered some of the costs involved in undertaking the course.

Although Morse no longer prescribes as often as she did while practising full-time in Alice Springs, she encourages all optometrists working in the Northern Territory to gain endorsement. 'Particularly if you're working in a smaller area, getting endorsed will be beneficial for you and the community,' she said.

'A therapeutically-endorsed optometrist practising in the Northern Territory would never find their prescription pad gathering dust.'

# Ocular nu

## Eat your way

**There has been resurgence in the use of vitamins and minerals to enhance our general health and the health of our eyes. In the USA more than 50 per cent of elderly people use some form of dietary supplement.**

An impressive body of research shows that nutritional support can make a difference in the development of eye conditions and that elderly people have different metabolic needs that must be met by using nutritional supplements.

For several years we have become familiar with the effect of free radical damage and how it is the principle cause of heart disease, cancer, cataracts and AMD. We have also learned about the antioxidant micronutrients, particularly vitamins A, C and E, which are the principle line of defence against oxidative degeneration.

With the 2001 publication of the Age-Related Eye Disease Study (ARED) in the USA, doctors began looking for more scientific information on the benefits of nutritional therapy.[1] The medical profession recognises that very few people get enough antioxidants and essential nutrients in their diet.[2]

### Micronutrients in eye health

Let's take a look at the various nutrients that are involved with eye health and disease control.

### Carotenoids

More than a dozen carotenoids have been found in blood, but only two specific xanthophyll carotenoids–lutein and zeaxanthin–accumulate in the fovea. The generally accepted functions of these two dietary xanthophylls are to provide macula pigment to filter blue light and the antioxidant activity (along with other job-specific antioxidants) that protects the eye against singlet oxygen radicals.[3,4]

We now believe that it is more likely that the macular pigment is entirely of dietary origin, and a recent study suggests that both healthy and diseased maculae can accumulate and stabilise levels of lutein and zeaxanthin. This is of particular interest for patients diagnosed with AMD, as well as for those who supplement their diets with these carotenoids to help prevent macular degeneration.[5]

### Cataracts and nutrients

Although there are several factors that contribute to the development of senile cataract, oxidative stress has been identified as an initiating factor. Nutritional antioxidants such as vitamin C, vitamin E, lycopene, lutein and zeaxanthin have been found to delay the development of experimental cataract.[6] Nutritional evaluation of cataractous lenses have shown an increase in water, sodium and calcium, while there is a corresponding decrease in protein, potassium, glutathione and ascorbic acid.

### Beta carotene

Beta carotene, most commonly included in supplements as a source of pro-formed vitamin A, converts to retinol only when and if the vitamin A cellular stores are retinol deficient. This conversion becomes increasingly difficult with ageing so a good source of vitamin A should be from retinol and not beta-carotene. One very well respected study indicates that excessive beta carotene can actually lead to AMD.[7]

### Vitamin C

Only after the baseline of essential nutrients is met on a daily basis is it safe to add individual nutrients in higher amounts for therapeutic purposes.[8] One example is the use of vitamin C. Many people supplement with very high doses of vitamin C because they have heard that the antioxidant and immune properties of vitamin C might prevent or shorten a bout with the cold or flu virus. This is not always wise. Vitamin C is a powerful diuretic that flushes out not only toxins (a beneficial effect), but also water-soluble nutrients such as the B-complex vitamins and many minerals. High doses of vitamin C can also have a laxative effect.

### Vitamin E

Scores of published studies strongly suggest that supplemental vitamin E acts as a potent antioxidant, maintaining the integrity of cell membranes as well as protecting the fats in low-density lipoproteins (LDLs) from oxidation. A recent analysis of vitamin E research concluded that vitamin E supplementation did not affect mortality rates overall.[9] There are eight different sub-categories of vitamin E, with the alpha-tocopherol being the most popular. Recent research has pointed to gamma-tocotrienol being an important player in cholesterol control and other metabolic functions.

### Antioxidants and reactive oxygen species

Oxidative damage with the unregulated production of reactive oxygen species (ROS) has been implicated in a growing list of clinical disorders such as macular degeneration, cataracts, arteriosclerosis, rheumatoid arthritis, cancer, stroke, Parkinson's disease and Alzheimer's disease. From a clinical perspective, it appears reasonable that combining several different antioxidant compounds in the composition of formulas offers a greater benefit than that provided by the use of single compound or even formulae containing a limited spectrum of antioxidant compounds.

### Minerals

Most manufacturers of multiple vitamins include the full spectrum of minerals that are necessary for the use of most vitamins and phytochemical antioxidants. Because minerals such as magnesium, sodium, copper and zinc compete metabolically, it can be harmful when too much of one mineral interferes with another. For example, long-term supplemental zinc can block absorption of copper, which is necessary for bone-marrow red cell production. It is

# trition
## to a healthy eye

**Dr Jeffrey Anshel** OD FAAO

strongly suggested that intake of excessive amounts of supplemental zinc is detrimental to overall body health, including the health of the brain and the prostate.[10-12]

## Carbohydrates

Carbohydrates have also received bad press recently due to the popularity of diet plans that promote a low-carbohydrate lifestyle. While this is well meaning and weight loss is an outcome of this type of diet, the long-term picture is not that of a healthy person.

Increasing the intake of simple carbohydrates into the human diet requires the pancreas to work harder because insulin is needed to manage the flood of glucose into the bloodstream. High levels of blood glucose (hyperglycemia) are toxic and must be cleared rapidly to maintain normal body function.

One problem they create is abnormal reactions of glucose with protein molecules (glycation) that can result in defective enzymes and tissues. Glycation may account for some of the degenerative changes commonly seen in diabetes such as vascular and retinal damage.

Complex carbohydrates are essential for overall health and energy production, while at the same time allowing for a slower release of insulin into the bloodstream. Review the glycaemic index (GI) at www.glycemicindex.com to see which foods have a high or low GI. Foods with a high GI peak insulin production too quickly and create glycation, whereas foods with a lower GI cause the release of insulin more slowly.

## Omega-6 fatty acids

Omega-6 fatty acids have been given a bad rap by well-meaning but misinformed medical writers. It is true that the typical diet is overloaded with omega-6 linoleic acid (LA) from vegetable oils such as sunflower, safflower, corn, cottonseed and soybean oils, which are added to nearly all processed foods. Many pantries are far too full of overly processed crackers, chips, cookies and cakes, as well as omega-6 oils that oxidise too quickly and become pro-inflammatories. Good health also depends on omega-6 gamma linolenic acid (GLA), which is a downstream metabolite of omega-6 linoleic acid, and is found in sources such a black currant seed oil, borage oil and evening primrose oil. This compound is a necessary component in the downstream metabolism of omega-6 fatty acid to the series one anti-inflammatory prostaglandin (PGE1). This is associated with healthy mucosal tissue and healthy tear film. The human body cannot metabolise omega-3 fatty acids to this specific anti-inflammatory prostaglandin.[13]

## A question of balance

If each nutrient is a part of the vastly complex human biochemistry, it makes sense to ensure that all the components in the infinite chemical balance of life are present so they can work together properly. Balance is more important than individual micronutrients.

In recent years, many studies of antioxidant therapy have focused on a single compound, both *in vitro* and *in vivo*. This approach does not provide an accurate reflection of the interactions between and among the various antioxidants as they occur in the intact cell, especially when using formulae containing compounds with different mechanisms of action and molecular targets. In terms of biological and antioxidant activity, the impact on the oxidant-antioxidant balance should be greater if the formulae being used contain a wider spectrum of antioxidant compounds than those containing a limited number of antioxidant compounds.

## Conclusion

It is not within the scope of this article to cover all micronutrients affecting the eye. It is important to remember that anything that affects the eye affects the entire body. The eye reflects the health of the body, with a number of specific target areas. The bottom line for optimal health is that everyone should avoid hydrogenated fats and eat a well-balanced diet that includes the currently recommended nine to 13 servings of fruits and vegetables a day. Because most people have challenges maintaining that ideal diet, using a well-rounded full spectrum multiple vitamin is usually necessary.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# Contact lenses offer

**More than 90 per cent of ocular drug delivery to the eye is through ophthalmic drops.[1] Although commonly used, ophthalmic drops are not an efficient means of delivering drugs to the eye, as less than seven per cent of active drug administered actually reaches the eye,[2] the rest is lost to the systemic circulation, potentially causing adverse side-effects.**

Patient compliance is also an issue; prescribed drops that are not taken due to ability, motivation or commitment may as well not have been prescribed at all. It is in this context that researchers have begun looking to contact lens materials as potential drug delivery devices.

It is estimated that there are more than 680,000 contact lens wearers in Australia,[3] many of whom have chronic or acute conditions that require concurrent administration of eye-drops. If their drugs could be delivered through contact lens wear, many patients' lives could be improved by alleviating the burden of taking eye-drops, and more importantly from a medical point of view, therapeutic targets would be more consistently achieved and conditions more appropriately managed.

**Dr Alex Hui** OD
**Dr Lyndon Jones**
FCOptom PhD

Since the introduction of highly oxygen permeable silicone hydrogel lenses in the late 1990s and the prospect of longer, safer contact lens wear, there has been renewed interest in the therapeutic use of contact lenses. For example, previous treatment of corneal abrasions involved ocular patching or use of older generation low oxygen permeable hydrogel lenses, which increased the risk of complications due to hypoxic overnight wear.[4] With more oxygen permeable materials, practice patterns changed as longer-term, lower-risk wear was achieved.[5]

> **The challenge that most researchers are facing is tailoring the release of the drug to occur at a constant, therapeutically relevant rate.**

The use of soft contact lenses as drug delivery devices was postulated as early as 1965[6] though they have been used only minimally in this capacity. Used for the treatment of glaucoma, Ocusert is the most widely known and successful commercially available ophthalmic drug delivery device. It is a pilocarpine soaked ocular system placed in the lower conjunctival sac. While effective in managing glaucoma, Ocusert suffers as a treatment strategy due to patient discomfort, lack of visual correction and the decrease in preferred practice patterns in prescribing pilocarpine.[7] A drug delivering contact lens must retain all of the properties of contact lenses, providing clear, safe and comfortable vision, while adding the ability to deliver therapeutic doses of the drug in question. Critically, the device should be able to deliver a constant, steady rate of drug so that the patient remains in the therapeutic window as long as treatment is needed.[1]

## Current research avenues

The simplest possible contact lens drug delivery device would merely modify commercially available materials. Given that much of the approval process by regulatory agencies has already been performed, these devices could potentially reach the market sooner. In their simplest form, these materials would merely be soaked in the drug of interest and then used by patients. Many commercially available silicone hydrogel and polyHEMA-based hydrogel lenses have been investigated as potential antibiotic (ciprofloxacin[8]) and anti-inflammatory (dexamethasone[9] and ketorolac[10]) delivering devices, by measuring both the uptake and release of the drug into solution.

Unfortunately, while the majority of materials tested are able to release therapeutically relevant amounts of drugs, most of the drug is released within the first 15 to 20 minutes. Research into the true modification of commercial materials centres around the creation of diffusion barriers, which slow the release of the drug from the material. Hydrophobic vitamin E was tested as a surface treatment to slow the release of hydrophilic timolol, fluconazole and dexamethasone phosphate. While the same quantity of drug was released as non-coated lenses, drug release time was extended to more than

# effective drug delivery

They are more efficient than eye-drops, alleviate issues of non-compliance and have wide-ranging application. Are contact lenses the future of drug administration?

100 hours from an untreated release time of only a few hours.[11]

There has been a push towards the creation of new, novel materials that can be tailored to specific drug release characteristics. Researchers have investigated many different types of surface modifications or additions, such as the addition of nanoparticles or pendent cyclodextrins, both of which serve to hold the drug on the surface of the lens, leading to longer release times.[12]

Much of the excitement within the field of ocular drug delivery centres on molecular imprinting. With this technique the drug to be delivered is present within the pre-polymerisation mixture along with a functional monomer.

After polymerisation, molecular memory or cavities that are physically and chemically conformational to the drug are created within the gel structure.[13] Because the drug is not attached to the gel covalently, it is still able to freely diffuse through the gel, but at a much slower pace as it interacts with custom cavities. Using this strategy, gels have been created to deliver hyaluronic acid[14] and the drugs norfloxacin,[15] timolol[16] and ketotifen.[17]

In the simplest imprinting experiments, imprinting allowed for at least twice as much loading and an extension of release from a few hours to well over a day.[15] Researcher continues to investigate the nature of the monomers or combination of monomers, which may increase the drug diffusion time.[2] Molecular imprinting remains a very flexible type of solution for drug delivery. There is the potential for very long release times of several days or even weeks through variation of the amount and strength of the association between the drug and the material memory.

The challenge that most researchers are facing is tailoring the release of the drug to occur at a constant, therapeutically relevant rate. Most of the materials so far exhibit an initial large burst of drug release, and decreasing release thereafter. In addition, molecular imprinting is a very specific process so only the drug that was imprinted into the gel will be able to load and employ slow release. Other drugs will interact with the material as if it was not imprinted.

## Patient benefits and commercialisation

Any individual who requires eye-drops while also wearing contact lenses is a potential beneficiary of drug delivering lenses. The lenses can be used in acute situations, such as antibiotic delivery during ocular infections or after corneal injury. The materials would be of great use post-surgically for such procedures as photorefractive keratectomy, where patients are already wearing a bandage lens for comfort while concurrently applying topical steroid and antibiotics hourly. If the bandage is able to deliver the medicine, these patients can be allowed to simply rest uninterrupted.

Finally, these devices would be of great use for chronic conditions such as glaucoma, allergy or dry eye. Even an allergy sufferer who does not require a refractive correction could potentially wear a contact lens that delivers sustained amounts of an anti-allergy drug to the eye, providing lasting, long-term comfort. Johnson & Johnson has completed phase 3 trials of an anti-allergy ketotifen-releasing lens, and future developments will inevitably result in the eventual commercialisation of ocular drug delivering contact lens devices.


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# Recurrent corneal

## Treatment includes ointment, bandage contact lenses and epithelial debridement

Many patients are scared of going to sleep at night for fear of waking up with ocular pain and extreme dry eye

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**Recurrent corneal erosions (RCE) usually occur secondary to corneal trauma or as a complication associated with map-dot and fingerprint dystrophy. About two per cent of the population have epithelial basement membrane dystrophy but the incidence of RCE in this group is about 10 per cent.**

RCE is characterised by sudden pain, lacrimation and photophobia on waking. The epithelial basal cells produce the basement membrane and the attaching fibrils that penetrate into the stroma. When this process is disrupted by either poor healing following trauma or by abnormal basement membrane in the presence of epithelial basement membrane dystrophy, microcysts and bullae form; the resultant localised oedema is thought to adhere to the palpebral conjunctive during sleep. Eye opening and/or eye movement then leads to a shearing off of the epithelium and the resultant symptoms.

Treatment of RCE mainly follows a well-established protocol. The initial treatment is usually a covering antibiotic ointment and cycloplegia if required, followed by the prolonged use of non-preserved lubricants during the day and ointment (Lacri-Lube) at night. The use of five per cent hypertonic saline ointment (Muro-128) has also been promoted as a means of controlling the oedema, but evidence suggests that it is no more efficacious than simple ointment.

Bandage contact lenses have also been used successfully to treat the condition. The main problem is that there is an increased risk of corneal infection due to extended wear and the necessity of a prolonged wearing time (12 to 24 weeks) requires frequent review, leading to increased cost.

Recalcitrant RCE can be treated successfully by epithelial debridement in the hope that the newly regenerating epithelium will produce a normal basement membrane. If this is unsuccessful, the treatment is expanded and may include micropuncture, photo-therapeutic keratectomy and excimer laser. The success rate of surgical intervention is between 90 and 100 per cent. The main disadvantages are post-surgical pain and cost.

A recent addition to the treatment of RCEs involves the use of oral doxycycline and topical steroid drops.[1] The doxycycline is dosed at 50 milligrams twice daily, and the steroid three times daily for a period of four weeks. This non-invasive technique has a success rate of about 80 per cent.

1. Wang L, Tsang H and Coroneo M. Treatment of recurrent corneal erosion syndrome using the combination of oral doxycycline and topical corticosteroid. *Clin Experiment Ophthalmol* 2008; 36: 1: 8-12.

# erosions

## Case report

## Non-invasive therapy solves ongoing problem

**A 37-year-old female presented with a history of a stick injury to the left eye six months previously.**

About one month following the trauma, she started to experience the classic symptoms of RCE and sought treatment. The accepted routine of daytime lubricants with the application of Lacri-Lube was prescribed by her practitioner, but she felt it had been ineffective as the eye would heal for a week or two and the problem would recur.

The main symptoms were those of an extremely dry left eye at night requiring the application of ointment at least three times during the night, and episodes of recurrent pain, lacrimation and photophobia on waking at about two-week intervals. As occurs in many patients who experience RCE, she was becoming scared of going to sleep at night in fear of the pain that could occur in the morning.

She had begun self-medication with Muro-128 for one month prior to her visit and reported no effective relief of symptoms. At presentation, routine eye examination revealed no abnormalities with the exception of the appearance of both corneae. Slitlamp examination revealed a stunning bilateral circumferential fingerprint corneal dystrophy in a band about two to three millimetres wide adjacent to the limbus (Figure). Also present in the left eye was a small area of negative staining, about one millimetre in diameter, slightly inferior and temporal to the pupil margin. A small spot of map-dot dystrophy was present at the level of the basement membrane.

As there was no corneal staining or epithelial defect, she was advised to continue with her current regimen and return if symptoms occurred. She returned 12 days later with an active RCE in the exact location of the area of negative staining. Topical non-preserved chloramphenicol 0.5% was applied as a covering antibiotic followed 10 minutes later by 0.5% cyclopentolate hydrochloride (cyclogyl). A bandage contact lens was inserted and the patient was reviewed on a regular basis for the following two weeks.

She found the pain relief afforded by the contact lens during the initial phase of the RCE to be extremely effective, but ongoing problems with daytime dryness and discomfort led to the lens being removed after two weeks. Lacri-Lube was prescribed for night-time use.

Two weeks later she presented with another episode of RCE, and the same treatment with a bandage lens initiated. Due to the history of this being a recalcitrant condition, I advised her of the other therapies available, but she was not keen to undergo surgical treatment, mainly due to the fear of post-operative pain.

We then decided to try oral doxycycline (50 milligrams twice daily) and topical fluoromethalone 0.1% Q4h. Both doxycycline and corticosteroids have been shown to inhibit the key metalloproteinases important to the condition's pathogenesis. I referred her to her GP for the oral medication. This was continued for a period of four weeks, over which time there was no recurrence of the condition. The patient reported a marked improvement in the symptoms of night-time dryness to the extent that the ointment was required only once, and she was able to sleep through the entire night without having to instill more lubricant. To date, it has been two months without a return of the RCE.

There are still questions[1] about the efficacy of this treatment compared to the standard use of lubricants but in this particular case it has been successful.

1. Watson SL, Barker NH. Interventions for recurrent corneal erosions. Cochrane Database of Systematic Reviews 2007, Issue 4 Art No: CD001861. DOI: 10.1002/14651858.CD001861.pub2

**Small section of the marked circumferential fingerprint dystrophy**

# PBS list of medicines for optometrists 16 August 2010

| | Product | Max qty | Repeats |
|---|---|---|---|
| **Antiglaucoma preparations** | | | |
| Betaxolol eye-drops, suspension, 2.5 mg (as hydrochloride)/mL, 5 mL | Betoptic S | 1 | 5 |
| Betaxolol eye-drops, solution, 5 mg (as hydrochloride)/mL, 5 mL | Betoptic | | |
| | BetoQuin | 1 | 5 |
| Bimatoprost eye-drops 300 mg/mL, 3 mL | Lumigan | 1 | 5 |
| Bimatoprost with timolol eye-drops containing 300 mg bimatoprost with timolol 5 mg (as maleate)/mL, 3 mL | Ganfort 0.3/5 | 1 | 5 |
| Brimonidine eye-drops containing brimonidine tartrate 2 mg/mL, 5 mL | Alphagan | | |
| | Enidin | 1 | 5 |
| Brimonidine with timolol eye-drops containing brimonidine tartrate 2 mg with timolol 5 mg (as maleate)/mL, 5 mL | Combigan | 1 | 5 |
| Brinzolamide eye-drops 10 mg/mL, 5 mL | Azopt | | |
| | BrinzoQuin | 1 | 5 |
| Dorzolamide eye-drops 20 mg (as hydrochloride)/mL, 5 mL | Trusopt | 1 | 5 |
| Dorzolamide with timolol eye-drops containing dorzolamide 20 mg (as hydrochloride) with timolol 5 mg (as maleate)/mL, 5 mL | Cosopt | 1 | 5 |
| Latanoprost eye-drops 50 micrograms/mL, 2.5 mL | Xalatan | 1 | 5 |
| Latanoprost with timolol eye-drops 50 micrograms latanoprost with timolol 5 mg (as maleate)/mL, 2.5 mL | Xalacom | 1 | 5 |
| Pilocarpine eye-drops containing pilocarpine hydrochloride 10 mg/mL, 15 mL | Isopto Carpine | | |
| | Pilopt | 1 | 5 |
| | PV Carpine | | |
| Pilocarpine eye-drops containing pilocarpine hydrochloride 20 mg/mL, 15 mL | Isopto Carpine | | |
| | Pilopt | 1 | 5 |
| | PV Carpine | | |
| Pilocarpine eye-drops containing pilocarpine hydrochloride 40 mg/mL, 15 mL | Isopto Carpine | | |
| | Pilopt | 1 | 5 |
| | PV Carpine | | |
| Pilocarpine eye-drops containing pilocarpine hydrochloride 60 mg/mL, 15 mL | Pilopt | 1 | 5 |
| | PV Carpine | | |
| Timolol eye-drops 2.5 mg (as maleate)/mL, 5 mL | Tenopt | | |
| | Timoptol | 1 | 5 |
| Timolol eye-drops 5 mg (as maleate)/mL, 5 mL | Tenopt | | |
| | Timoptol | 1 | 5 |
| Timolol eye-drops (gellan gum solution) 2.5 mg (as maleate)/mL, 2.5 mL | Timoptol XE | 1 | 5 |
| Timolol eye-drops (gellan gum solution) 5 mg (as maleate)/mL, 2.5 mL | Timoptol XE | 1 | 5 |
| Timolol eye gel 1 mg (as maleate)/g, 5 g | Nyogel | 1 | 5 |
| Travoprost eye-drops 40 micrograms/mL, 2.5 mL | Travatan | 1 | 5 |
| Travoprost with timolol eye-drops 40 micrograms travoprost with timolol 5 mg (as maleate)/mL, 2.5 mL | Duotrav | 1 | 5 |

**By writing a PBS prescription for an antiglaucoma agent, the prescriber is certifying that the criteria set out in the PBS guidelines are satisfied**

| | Product | Restriction | Max qty | Repeats |
|---|---|---|---|---|
| **Anti-viral eye preparations** | | Restricted: | | |
| Aciclovir eye ointment 30 mg per g (3%), 4.5 g | Zovirax | Herpes simplex keratitis | 1 | 0 |
| **Antibiotics** | | Unrestricted | | |
| Chloramphenicol eye-drops 5 mg/mL (0.5%), 10 mL | Chlorsig | | 1 | 2 |
| | Chloromycetin | | 1 | 2 |
| Chloramphenicol eye ointment 10 mg/g (1%), 4 g | Chlorsig | | 1 | 0 |
| | Chloromycetin | | 1 | 0 |
| Framycetin sulfate eye-drops 5 mg/mL (0.5%), 8 mL | Sofracycin | | 1 | 2 |
| Sulfacetamide sodium eye-drops 100 mg per mL (10%), 15 mL | Bleph-10 | | 1 | 2 |
| **Anti-inflammatory agents** | | Unrestricted | | |
| Fluorometholone eye-drops 1mg/mL (0.1%), 5 mL | Flucon | | 1 | 0 |
| | FML Liquifilm | | 1 | 0 |
| Fluorometholone acetate eye-drops 1 mg/mL (0.1%), 5 mL | Flarex | | 1 | 0 |
| Flurbiprofen sodium eye-drops 300 µg/mL (0.03%) single dose units 0.4 mL, 5 | Ocufen | | 1 | 0 |
| Hydrocortisone acetate eye ointment 10 mg/g (1%), 5 g | Hycor | | 1 | 0 |
| **Anti-allergy agents** | | Restricted: | | |
| Sodium cromoglycate eye-drops 20 mg/mL (2%), 10 mL | Cromolux | Vernal keratoconjunctivitis | 1 | 5 |
| | Opticrom | | 1 | 5 |

**Continued**

| | Product | Restriction | Max qty | Repeats |
|---|---|---|---|---|
| **Tear supplements** | | Restricted: | | |
| Carbomer eye gel 2 mg/g (0.2%), 10 g | Geltears | Severe dry eye including | 1 | 5 |
| | PAA | Sjögren's syndrome | 1 | 5 |
| | Viscotears Liquid Gel | | 1 | 5 |
| Carmellose sodium with glycerin eye-drops 5 mg-9 mg per mL (0.5%-0.9%), 15 mL | Optive | | 1 | 3 |
| Carmellose sodium eye-drops 10 mg/mL (1%), 15 mL | Refresh Liquigel | | 1 | 5 |
| Carmellose sodium eye-drops 5 mg/mL (0.5%), 15 ml | Refresh Tears plus | | 1 | 5 |
| Hypromellose eye-drops 3 mg/mL (0.3%), 15 mL | In a Wink Moist'ing | | 1 | 5 |
| (contains sodium perborate) | Genteal | | 1 | 5 |
| Hypromellose eye-drops 5 mg/mL (0.5%), 15 mL | Methopt | | 1 | 5 |
| Hypromellose with carbomer 980 ocular lubricating gel 3 mg-2 mg/g (0.3-0.2%), 10 g | HPMC PAA | | 1 | 5 |
| | Genteal gel | | 1 | 5 |
| Hypromellose with dextran eye-drops 3 mg-1 mg/mL (0.3%-0.1%), 15 mL | Poly-Tears | | 1 | 5 |
| | Tears Naturale | | 1 | 5 |
| Polyethylene glycol 400 with propylene glycol drops 4 mg-3 mg/mL (0.4-0.3%); 15 mL | Systane | | 1 | 5 |
| Polyethylene glycol 400 eye drops 2.5 mg per mL (0.25%), 15 mL | Blink Intensive Tears | | 1 | 5 |
| Polyvinyl alcohol eye-drops 14 mg/mL (1.4%), 15 mL | PVA Tears | | 1 | 5 |
| Polyvinyl alcohol eye-drops 30 mg/mL (3%), 15 mL | PVA Forte | | 1 | 5 |
| Polyvinyl alcohol eye-drops 14 mg/mL (1.4%), 15 mL | Liquifilm Tears | | 1 | 5 |
| Polyvinyl alcohol eye-drops 30 mg/mL (3%), 15 mL | Liquifilm Forte | | 1 | 5 |
| Polyvinyl alcohol eye-drops 14 mg/mL (1.4%), 15 mL (contains sodium chorite/hydrogen peroxide as preservative) | Vistil | | 1 | 5 |
| Polyvinyl alcohol eye-drops 30 mg/mL (3%), 15 mL (contains sodium chorite/hydrogen peroxide as preservative) | Vistil Forte | | 1 | 5 |
| **Unpreserved tear supplements** | | Authority required: | | |
| Carbomer 974 ocular lubricating gel 3 mg/g (0.3%), single dose units 0.5 g, 30 | Poly Gel | Severe dry eye syndrome in patients sensitive to | 3 | 5 |
| Carbomer eye-gel 2 mg per (0.2%) , single dose units 0.6 mL, 30 | Viscotears | preservatives in multi-dose eye-drops | 3 | 5 |
| Carmellose sodium eye-drops 5 mg/mL (0.5%), single dose units 0.4 mL, 30 | Cellufresh | | 3 | 5 |
| Carmellose sodium eye-drops 10 mg/mL (1%) , single dose unit 0.4 mL, 30 | Celluvisc | | 3 | 5 |
| Carmellose sodium eye-drops 2.5 mg/mL (0.25%), single dose units, 0.6 mL, 24 | TheraTears | | 4 | 5 |
| Carmellose sodium ocular lubricating gel 10 mg/mL (1%), single dose 0.6 mL, 28 | TheraTears | | 3 | 5 |
| Hypromellose with dextran eye-drops 3-1 mg/mL (0.3-0.1%), single 0.4 mL, 28 | Bion Tears | | 3 | 5 |
| Polyethylene glycol 400 with propylene glycol drops 4 mg-3 mg/mL (0.4-0.3%); single dose units 0.8 mL, 28 | Systane | | 2 | 5 |
| Polyethylene glycol 400 eye drops 2.5 mg per mL (0.25%), single dose units 0.4 mL, 20 | Blink Intensive Tears | | 5 | 5 |
| Soy lecithin eye spray 10 mg/mL (1%), 10 mL | Tears again | | 2 | 5 |
| **Topical ocular lubricant ointments** | | Unrestricted | | |
| Paraffin compound eye ointment 3.5 g | Polyvisc | | 2 | 5 |
| | Duratears | | 2 | 5 |
| Paraffin pack containing 2 tubes compound eye ointment 3.5 g | Polyvisc (2 pack) | | 1 | 5 |
| Paraffin pack containing 2 tubes compound eye ointment 3.5 g | Ircal (2 pack) | | 1 | 5 |
| | Lacri-Lube (2 pack) | | 1 | 5 |

# Commercially available controlled substances that may be used or prescribed by optometrists

16 August 2010

| Ocular medicine | VIC | NT | SA | NSW | ACT | TAS | QLD | WA* | PBS Optometry | PBS Listed |
|---|---|---|---|---|---|---|---|---|---|---|
| **Anti-infectives** | | | | | | | | | | |
| Chloramphenicol | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Ciprofloxacin | ✓ | ✓ | ✓ | ✓ | – | ✓ | ✓ | – | – | ✓ |
| Framycetin | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | – | ✓ | ✓ |
| Gentamicin sulfate | ✓ | ✓ | ✓ | ✓ | – | ✓ | ✓ | – | – | ✓ |
| Ofloxacin | ✓ | ✓ | ✓ | ✓ | – | ✓ | ✓ | – | – | ✓ |
| Sulfacetamide | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Tetracycline | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | – | N/L | N/L |
| Tobramycin | ✓ | ✓ | ✓ | ✓ | – | ✓ | ✓ | – | – | ✓ |
| Aciclovir | ✓ | ✓ | ✓ | ✓ | – | ✓ | ✓ | – | ✓ | ✓ |
| **Anti-inflammatories** | | | | | | | | | | |
| Dexamethasone | ✓ | ✓ | ✓ | ✓ | – | ✓ | ◆ | – | – | ✓ |
| Fluorometholone | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | – | ✓ | ✓ |
| Fluorometholone acetate | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | – | ✓ | ✓ |
| Hydrocortisone | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | – | ✓ | ✓ |
| Prednisolone | ✓ | ✓ | ✓ | ✓ | – | ✓ | ◆ | – | – | ✓ |
| Diclofenac | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | – | N/L | N/L |
| Flurbiprofen | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | – | ✓ | ✓ |
| Ketorolac | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | – | N/L | N/L |
| **Decongestants, anti-allergics and astringents** | | | | | | | | | | |
| Antazoline | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | N/L | N/L |
| Ketotifen | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | N/L | N/L |
| Levocabastine | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | N/L | N/L |
| Lodoxamide | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | N/L | N/L |
| Naphazoline | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | N/L | N/L |
| Olopatadine | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | – | N/L | N/L |
| Pheniramine | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | N/L | N/L |
| Sodium cromoglycate | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Tetrahydrozoline | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | N/L | N/L |
| **Anti-glaucoma preparations** | | | | | | | | | | |
| Apraclonidine | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ◆ | – | – | ✓ |
| Betaxolol | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ◆ | – | ✓ | ✓ |
| Bimatoprost | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ◆ | – | ✓ | ✓ |
| Brimonidine | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ◆ | – | ✓ | ✓ |
| Brinzolamide | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ◆ | – | ✓ | ✓ |
| Dorzolamide | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ◆ | – | ✓ | ✓ |
| Latanoprost | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ◆ | – | ✓ | ✓ |
| Pilocarpine | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ◆ | – | ✓ | ✓ |
| Timolol | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ◆ | – | ✓ | ✓ |
| Travoprost | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ◆ | – | ✓ | ✓ |
| Timolol+Bimatoprost | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ◆ | – | ✓ | ✓ |
| Timolol+Brimonidine | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ◆ | – | ✓ | ✓ |
| Timolol+Dorzolamide | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ◆ | – | ✓ | ✓ |
| Timolol+Latanoprost | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ◆ | – | ✓ | ✓ |
| Timolol+Travoprost | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ◆ | – | ✓ | ✓ |
| **Mydriatics and cycloplegics** | | | | | | | | | | |
| Atropine | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | – | – | ✓ |
| Cyclopentolate | ✓ | ✓ | ✓ | ✓ | ✓ | D | ✓ | D | N/L | N/L |
| Homatropine | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | – | – | ✓ |
| Pilocarpine | ✓ | ✓ | ✓ | ✓ | – | ✓ | ✓ | – | – | ✓ |
| Phenylephrine | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | – | N/L | N/L |
| Tropicamide | ✓ | ✓ | ✓ | ✓ | ✓ | D | ✓ | D | N/L | N/L |
| **Local anaesthetics** | | | | | | | | | | |
| Amethocaine | ✓ | ✓ | ✓ | ✓ | ✓ | D | ✓ | – | N/L | N/L |
| Lignocaine | ✓ | ✓ | ✓ | ✓ | – | D | – | – | N/L | N/L |
| Oxybuprocaine | ✓ | ✓ | ✓ | ✓ | ✓ | D | ✓ | D | N/L | N/L |
| Proxymetacaine | ✓ | ✓ | ✓ | ✓ | ✓ | D | ✓ | D | N/L | N/L |

◆ The use of these medicines by optometrists is currently being considered
* Optometrists in Western Australia do not have access to the PBS
D Diagnostic use only
N/L Substance is not listed under the PBS

PBS LISTED
1st August 2010

# Find comfort in our strength[1,2,3]

**New AZARGA® Suspension brings you the strength you expect with the comfort your patients deserve.[1,2,3]**

- **AZARGA®** Suspension lowers mean IOP by up to 9.1 mm Hg from baseline.[1] (p<0.0001)
- Significantly more comfort than COSOPT* Solution.[†2,3] (p=0.0003)
  [†]Mean discomfort scores for COSOPT* were double those for **AZARGA®** Suspension
- When you select a tCAI combination, choose **AZARGA®** Suspension.

AZARGA®
(brinzolamide 1% & timolol 0.5%) eye drops, suspension

PBS Information: Restricted benefit. Reduction of elevated intra-ocular pressure in patients with open-angle glaucoma and ocular hypertension who are not adequately controlled with monotherapy

**PLEASE REVIEW PRODUCT INFORMATION, AVAILABLE ON REQUEST, BEFORE PRESCRIBING**

**PBS Dispensed Price: $27.49**

**MINIMUM PRODUCT INFORMATION AZARGA® (brinzolamide 1% & timolol 0.5%) EYE DROPS. INDICATION:** Decrease of intraocular pressure in patients with open-angle glaucoma or ocular hypertension for whom monotherapy with either component provides insufficient intraocular pressure reduction. **DOSE:** One drop twice daily in affected eye(s). **CONTRAINDICATIONS:** Hypersensitivity to any ingredients; bronchial asthma (and history) or severe COPD; sinus bradycardia; 2nd or 3rd degree atrioventricular block; severe allergic rhinitis and bronchial hyperreactivity; cardiac failure; cardiogenic shock; hyperchloraemic acidosis; severe renal impairment. **PRECAUTIONS:** Beta blocker and sulphonamide systemic effects: acid base disturbances, cardiovascular/respiratory reactions; anaphylaxis; spontaneous hypoglycaemia; insulin-dependent diabetes, hyperthyroidism; prinzmetal angina; severe circulatory disorders; hypotension; narrow-angle glaucoma; pseudoexfoliative glaucoma; pigmentary glaucoma; compromised corneas; contact lenses; pregnancy (category C); lactation; children. **Drug Interactions:** concomitant beta-blocker or carbonic anhydrase inhibitors use not recommended. **ADVERSE EFFECTS:** Common (≥1% to <10%): blurred vision, eye pain, eye irritation, foreign body sensation in eyes, dysgeusia. Less frequent adverse effects are listed in the AZARGA® Product Information. TGA approved 23 December 2009. Please review full approved Product Information before prescribing - available on request from Alcon Laboratories (Australia) Pty Ltd. *Trademark is the property of its owner.

**References: 1.** Manni G, Denis P, Chew P *et al. J Glaucoma* 2009; **18**(4): 293-300. **2.** Mundorf TK, Rauchman SH, Williams RD *et al. Clin Ophthalmol* 2008; **2**(3):623-8. **3.** Vold SD, Evans RM, Stewart RH *et al. J Ocul Pharmacol Ther* 2008; **24**(6):601-5. ® Registered Trademark.

Alcon Laboratories (Australia) Pty Ltd. 25 Frenchs Forest Rd. Frenchs Forest NSW 2086. POPH1961

Alcon®

ZADITEN®
ketotifen eye drops, 0.025%

# POWERFUL DEFENCE AGAINST ALLERGY EYES[1,2]

- **Triple mechanism of action**[1,3]
  - Antihistamine[4*]
  - Mast cell stabiliser[5*]
  - Eosinophil inhibitor[6*]
- **Relieves ocular itching within minutes**[1,3]
- **Protects against symptoms for up to 12 hours**[1,7]
- **Suitable for children 3 years and older**[1,8]
- **Also available in preservative-free single dose units**[1]


* All studies were conducted in vitro

**Always read the label. Use only as directed. If symptoms persist see your doctor/healthcare professional.**

**Please refer to the Product Information, available upon request, before recommending.**
Product Information is available from Novartis Pharmaceuticals Australia Pty Limited or visit www.novartis.com.au.
Zaditen eye drops are indicated for symptomatic short-term treatment of seasonal allergic conjunctivitis in adults and children 3 years or older. Dosage: one drop of Zaditen into the conjunctival sac twice daily. **References: 1.** Zaditen Product Information. **2.** Ganz M, Koll E, Gausche J et al. Adv Ther 2003; 20(2):79-91. **3.** Abelson MB, Ferzola NJ, McWhirter CL et al. Pediatr Allergy Immunol 2004:15:1-7. **4.** Sharif NA, Xu S, Yanni M. Drug Dev't Research 1994;33:448-453. **5.** Schoch C. J Ocul Pharmacol Ther 2003:19(1):75-81. **6.** Woerly G, Loiseau S, Loyens M et al. Allergy 2003:58:397-406. **7.** Greiner JV, Minno G. Clin Therap 2003:25(7):1988-2005. **8.** Abelson MB, Chapin MJ et al. Adv in Ther 2002:19(4):161-169.
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