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March 2019
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ADVANCING OPTOMETRY

Glaucoma in a new era

What should—and shouldn't—be done when confronting this sight-eclipsing condition?

Acute angle closure

A New Zealand approach

Ocular surface disease

Managing the side-effects of topical medications

IOP medication guide

A complete list of eye drops for your practice wall

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Optometry AUSTRALIA

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March 2019 Glaucoma and collaborative care

From the Editors

With World Glaucoma Week (10-16 March 2019) encouraging patients to have regular eye examinations, it is more important than ever that optometrists remember to take a collaborative care approach to ensure they are providing the best possible care.

'Collaborative care in glaucoma' encompasses the relationship between practitioner and patient. Helping your glaucoma patients maintain their eye drop regimen is vital to ensuring successful treatment of glaucoma; other co-morbidities, such as dry eye may provide further challenges for the patient.

As optometrist-turned-ophthalmologist Dr Nick Toalster points out in his article 'Drop toxicity and at-risk ocular surfaces,' it's important to listen to your patients and possibly alter their topical drop regimen if it seems the burden is too much for them.

Further, the phrase 'collaborative care in glaucoma' rightfully evokes cooperation between optometrists and ophthalmologists. Of course, each optometrist has their own level of confidence in managing their glaucoma patients. Regardless, all optometrists are expected to capably diagnose and identify the signs of glaucoma.

As Dr Joseph Sowka points out in his article in this issue 'Mistakes not to make in glaucoma management,' there are some common errors that can be avoided to make glaucoma diagnosis and management less arduous.

To further assist you in your own treatment protocols, we've included an IOP drug management table based on Optometry Australia's glaucoma clinical practice guide. And Dr Jack Phu from the Centre for Eye Health provides a helpful clinical guide in 'Glaucoma management for optometrists in 2019.'

Finally, in recognition of Optometry Australia's recently-released clinical practice guide on the treatment of age-related macular degeneration, Dr Angelica Ly explores a series of clinical strategies to supercharge the way you diagnose, understand and manage AMD.

This issue of *Pharma* offers 6 (5T) CPD points.

Access the online CPD modules at www.optometry.org.au

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Mistakes not to make in glaucoma management

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Diagnosing and managing patients with glaucoma can be a challenging task. Glaucoma can be diagnosed by observations of characteristic changes in the optic disc and retinal nerve fibre layer (RNFL), abnormalities in threshold perimetry, alterations in structure demonstrated on optical coherence tomography (OCT) and assessment of risk factors such as intraocular pressure (IOP) and family history of the disease.[1] Therapeutic intervention is generally straightforward; that is, reduction of IOP with medicines, lasers and/or surgery. However, errors in diagnosis and therapeutics can make glaucoma management an arduous task. Take care not to make these common errors

Mistake #1: Not recognising when the OCT is wrong

There are several issues in imaging that make OCT assessments for glaucoma very suspect and even misleading. A relatively limited normative database (against which the patient's measurements are compared), signal quality, blinks and saccades, segmentation errors, media opacities and an abnormal axial length can all contribute to induced false measurements on an OCT.

When interpreting an OCT printout, ensure that the quality score (as indicated for each specific proprietary device) has been met at a minimum. Look to see that there is proper illumination and clarity of focus and the optic disc image is properly centred with no missing data. Inspect the scan for signs of eye movement. Look to see how the device has segmented the individual layers to ensure that no artificial errors have been introduced. Posterior vitreous detachments and other vitreal issues may confuse the device and make it seem that it is measuring tissue that isn't really there. Finally, if using any macular scans or ganglion cell analysis measurements, ensure that there is no concurrent macular disease. If there is, then do not use this potentially misleading information.[2-4] (Figures 1 and 2.)

Mistake #2: Treating 'red disease'

Most OCT printouts colour-code results as to degree of statistical significance. Common coding uses green to connote the patient's measured data to be within 95 per cent confidence intervals, red to indicate when findings would occur normally in just one per cent of the population, and yellow to indicate all intervening values with borderline significance. In that each OCT manufacturer employs a relatively limited normative database to compare against, there commonly will be situations where a patient's measured data falls outside the device's normative database, yet the patient may be completely healthy and normal. Just because a patient's measured information falls outside the 99 per cent level doesn't mean that there is disease present. In this instance, much of the printout will be coded as abnormal in red, yet there is truly no disease present. This is commonly

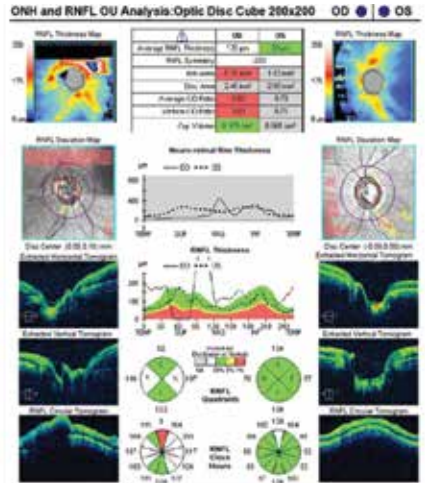


Figure 1. Abnormal OCT due to missing data from blink. Note how the RNFL thickness superiorly drops to '0.' This never happens anatomically and is a result of the missing data rather than true glaucomatous loss.

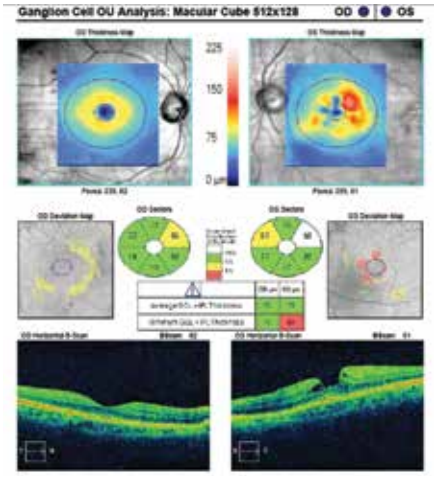


Figure 2. Abnormal ganglion cell analysis OS due to epiretinal membrane and macular pseudo-hole. Such images of concurrent disease should not be used in glaucoma analyses.

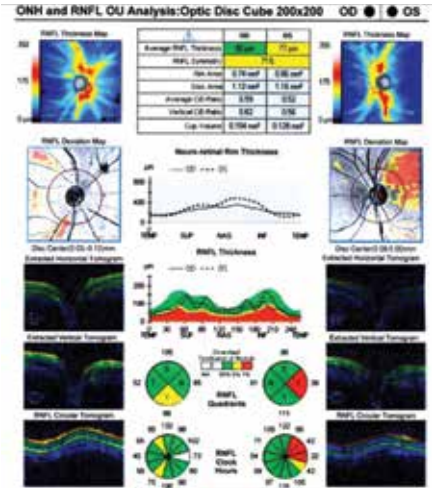
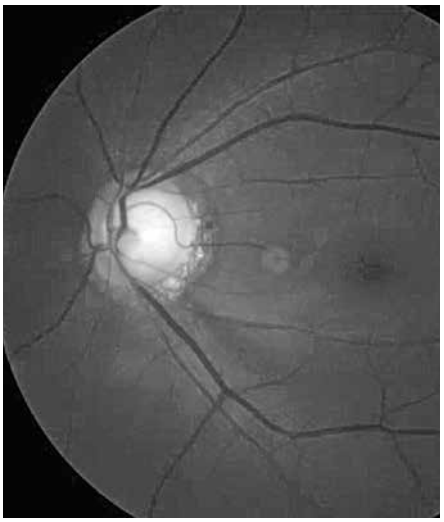
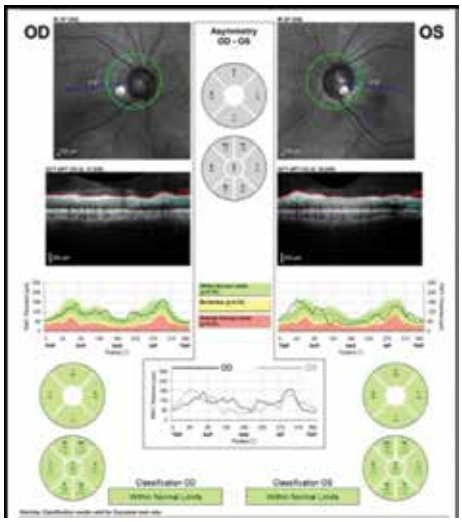


Figure 3. Left superior temporal OCT abnormality in an eye with a robust OCT thickness map, normal visual field, and ophthalmoscopically normal optic disc and RNFL as an example of 'red disease'

referred to as 'red disease.'[5]

The use and overemphasis of imaging technology to the exclusion of additional clinical findings and assessment of risk will put patients in peril. All imaging technology must be interpreted in context with other clinical findings and when the OCT results do not fit with known correlates of glaucoma, the results should be interpreted with caution (Figure 3).





Figures 4. A: An ophthalmoscopically visible RNFL defect. B: A normal OCT with all data falling within the device's normative database in a classic example of 'green disease.'

Mistake #3: Not treating 'real disease'

Similar to red disease discussed above, there may be instances where patient data may fall within the OCT normative confidence interval with results printed in green, yet have clinically, ophthalmoscopically visible damage to the RNFL and functional loss on threshold perimetry.[6] This commonly occurs when inspecting the quadrant and clock hour graphs on OCT. When the RNFL analysis is divided into four quadrants or 12 clock hours, it must be remembered that considerable area is being averaged to give these sector values. A focal RNFL defect may be present ophthalmoscopically, but when averaged in with adjacent healthy tissue on OCT, the value may fall within the device's normative database. Thus, everything is printed in green, giving a false sense of security in an eye that truly has structural damage. Thus, it is important to weigh the OCT results against the optic disc photographs and clinical examination to ensure that "green disease" is not missed[7] (Figures 4A – B).

Mistake #4: Changing therapy based upon one bad IOP reading or one changed visual field

Intraocular pressure measurements and visual field results can be variable, especially when one considers patient compliance with medications and the psychophysical responses in threshold perimetry. Patients often overstate adherence to medical therapy. Even when not trying to be intentionally misleading, many patients may not correctly remember if they used their medication properly immediately before the examination. Medicines don't fail overnight. A medically adherent patient will not have an IOP of 15 mmHg on one visit and 30 mmHg on the next visit due to medicine failure or progressing trabecular dysfunction.

There will be a slow, progressive upward drift of IOP in cases where medicines are failing to control IOP. Always insist at least two IOP readings above target (and preferably three) before making any therapeutic changes. Similarly, visual field changes occur frequently, but shouldn't be considered progression unless the change is verified in a subsequent (and preferably two) visual fields. Over 80 per cent of abnormal visual fields noted in the Ocular Hypertension Treatment Study were not verified on repeat testing.[8] Always look for a sustained decrease in visual field results before changing therapy.

Mistake #5: Not getting enough pre-treatment... and post-treatment IOPs

Unless a patient presents with very high IOP (above 45 mmHg) or has advanced disease (with loss of central visual acuity or relative afferent pupil defect in an eye), there is generally no need to rush to treat chronic open angle glaucoma. It is very beneficial to get several IOP readings (at least two and preferably three) before initiating treatment of any kind. At one visit, the patient may be exhibiting a peak IOP or a trough reading. Knowing the range is very important.[9] Similarly, one should never prematurely judge efficacy of treatment based upon the IOP reading immediately after initiation of therapy.

Even if the first IOP measurement after initiating therapy isn't impressively lowered, consider leaving therapy unchanged and check at least one more time before deciding if a medication is truly efficacious or not. In the example here, there was an abrupt IOP drop after the initiation of therapy. However, it is notable that there are several pre-treatment IOPs that are nearly identical to the post-treatment IOPs, indicating that the prescribed medication, while overall effective, doesn't consistently give the robust pressure reduction initially seen (Figure 5).

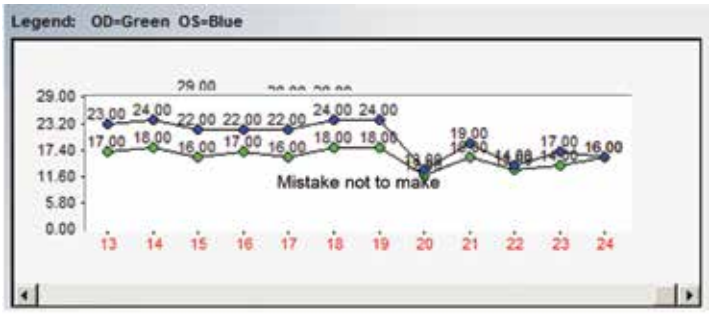


Figure 5. IOP curve before and after treatment initiation for glaucoma. Several pre-treatment IOPs were nearly identical to post-treatment IOPs, raising questions about the effectiveness of the chosen therapy.

Continued page 4

Mistakes to avoid

From page 3

Mistake #6: Not recognising a neurologic visual field in a glaucoma patient

One of the most insidious situations in eye care occurs when a patient with glaucoma manifests a neurologic disease concurrently. While glaucoma causes arcuate visual field defects that respect the horizontal meridian and neurologic conditions cause hemianopic defects that respect the vertical meridian, such patterns can get lost within the same patient. There are two ways to discern these differences. First, a glaucomatous visual field can be predicted by the optic disc and RNFL appearance. When the field loss is greater than expected and, often in an area not anticipated based upon the optic disc appearance, one should look for the neurogenicity by examining carefully both visual fields. Additionally, the greyscale printout is exceptional at identifying visual field defects which respect the vertical meridian while the pattern deviation can be quite poor. Further, while glaucomatous and neurologic damage can occupy the same quadrant, neurological defects may actually manifest a deeper scotoma within a glaucomatous defect.

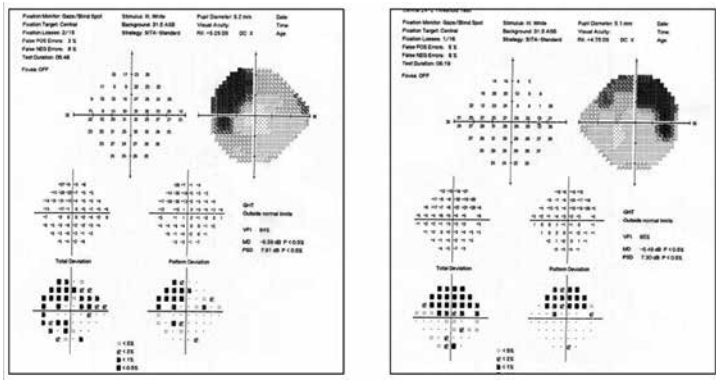


Figure 6. Superior bitemporal visual field defect in a patient with both glaucoma and pituitary macroadenoma. Note that the neurologic field is better appreciated on the grey scale than on the pattern deviation.

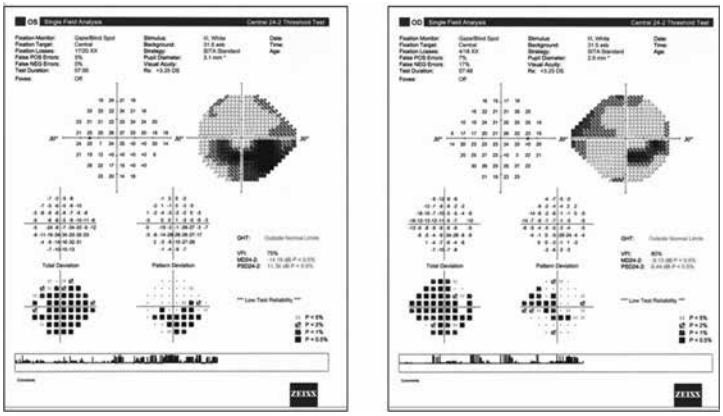


Figure 7. Right inferior quadrant defect hidden beneath the glaucomatous losses. Note that the neurologic field is better appreciated on the grey scale than on the pattern deviation.

CASE REPORT

A 74-year-old female previously diagnosed with glaucoma had optic nerve and RNFL damage consistent with glaucoma. However, observation of the grey scale showed bitemporal visual field defects that respected the vertical meridian. The fields were repeated and the pattern persisted. Ultimately, she was diagnosed with a pituitary macroadenoma and scheduled for neurosurgical intervention (Figure 6).

A second patient, a 65-year-old female also previously diagnosed with glaucoma exhibited bilateral inferior defects on visual fields. The left visual field matched extreme superior disc damage in that eye. In the right eye, her superior field defect matched optic disc and RNFL damage, but there was no structural abnormality to explain her inferior visual field loss. Most notable was the fact that the right inferior visual field defect stopped at the vertical meridian on the grey scale in the right eye. While the left eye had a significant inferior arcuate scotoma, it was notable that the left inferior nasal defect was absolute and much deeper than the remainder of the field loss. This led to the observation that she had not only glaucomatous arcuate visual field defects, but also a superimposed right inferior quadrantanopia. Subsequent neuroimaging revealed an ischemic cerebral infarct (Figure 7).

Glaucoma diagnosis and management can be quite challenging. It is important to be aware that there are common errors that can make glaucoma management much more challenging.

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Recent advances in minimally-invasive glaucoma surgery

The rise of MIGS and the promise of drop-free IOP-lowering treatment with less risk

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A string of recent innovations have seen a rise in the development of glaucoma drainage devices, namely MIGS.

Variously referred to as 'minimally' or 'micro' invasive glaucoma surgery, MIGS devices are now in the spotlight as a viable and less-invasive option than penetrating glaucoma surgery, to assist in lowering intra-ocular pressure in glaucoma patients.

Optometry is at the forefront of primary patient care, and optometrists are increasingly managing a growing number of glaucoma patients. With the advent of MIGS devices, it's important for optometrists to understand the landscape of MIGS surgery, including available devices, indications for their use, identifying suitable patients and recognising potential complications.

The topic of MIGS devices is very broad, and a comprehensive analysis is not possible within the scope of this article. Ultimately, the goal of these devices is to lower intraocular pressure (IOP) in patients with open angle glaucoma, when medical therapies alone are inadequate, or, in suitable patients, where an alternative option can be undertaken at the time of cataract surgery.

CASE REPORT

The following case example illustrates the pivotal role of the optometrist in helping guide and manage MIGS options for patients.

Mrs NA is a 72-year-old female with right eye primary open angle glaucoma (POAG), uncontrolled on dual drop therapy including prostaglandin analogue and a carbonic anhydrase inhibitor. She has restricted mobility due to spinal problems, and suffers from asthma and heart disease, which precludes her from beta-blocker eye drops. She had tried alpha-antagonists, but was highly intolerant of them. Mrs NA lives in a small town, and my practice (an hour away) was the nearest ophthalmic service available to her. She'd previously undergone laser trabeculoplasty which was only modestly effective.

She was referred by her optometrist to help manage her glaucoma and cataracts. Mrs NA was noted as having increasing difficulty with drop toxicity despite preservative-free options, and her husband—who was helping instil the drops—has been increasingly unable to assist due to his declining health. Her referring optometrist, who had some experience in co-managing glaucoma patients, had discussed treatment options with her, including MIGS devices and penetrating glaucoma surgery combined with cataract surgery.

On presentation at my practice, her best corrected visual acuity (BCVA) was 6/12 in each eye due to moderate nuclear and cortical cataracts. Goldmann IOPs were 18-20 mmHg in her right eye, and 14 mmHg in her left eye. Her corneas were of normal thickness, and her angles were open on gonioscopy, with clear media and good visualisation of the angle structures. Her optic discs showed moderate cupping with an inferior notch in her right eye, and cup-to-disc ratio (CDR) measuring 0.8 compared to a normal left optic disc with CDR 0.3. Maculae were healthy. On Humphrey 24-2 perimetry, her right eye was affected by a reproducible superior arcuate scotoma and an inferior advancing nasal step, while her left visual field (VF) was normal. The findings were supported by OCT, with retinal

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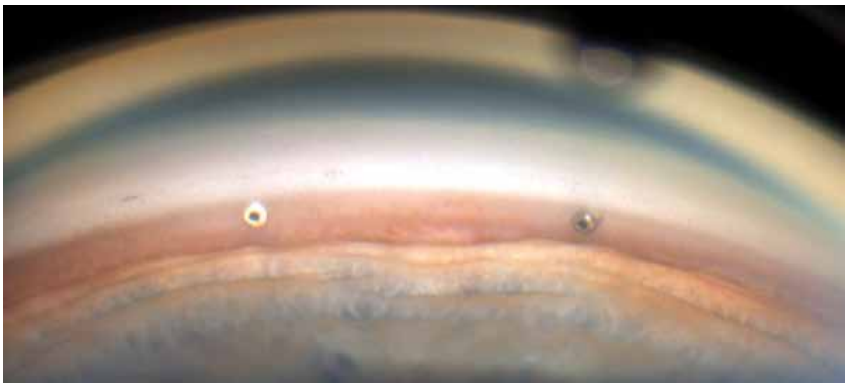

Figure 1. Two iStent injects are deployed into the trabecular meshwork

MIGS

From page 5

nerve fibre layer (RNFL) thinning and ganglion cell loss noted in the glaucomatous right eye.

Thanks to the informative discussion with her optometrist, Mrs NA had already thought about her treatment options. As she had limited mobility and comorbidities, she did not wish to undergo any invasive procedures that carry higher risks of complications, or any procedures that may require further management such as needling, effectively ruling out penetrating surgery and Xen Gel stent.

The options of trans-trabecular and supraciliary devices were discussed with her in detail. For ease of insertion, minimal risk of complications and likely least aftercare requirements, she opted for iStent injects combined with cataract surgery, aware that this would not be as efficacious as the more invasive options, but reassured by the fact that her post-operative care would likely be the least onerous.

She underwent her procedures successfully with cataract surgery combined with two iStent injects deployed into the nasal trabecular meshwork via gonio-prism visualisation (Figure 1). The expected amount of mild blood reflux was noted from Schlemms canal, which indicated good placement of the devices.

On day two post-operatively, her right eye vision was 6/9, and Goldmann IOP was 14 in the absence of pressure-lowering drops. There was mild microhyphaema, otherwise symptoms were minimal.

She was instructed to continue with her post-operative anti-inflammatory and antibiotic drops, without modifying usual post-cataract treatment. Due to travel logistics, I discussed her management with her local referring optometrist, who was happy to see her at one and two weeks after surgery. Fortunately, her IOP remained under 15, with distance vision improving to 6/6 and no complications otherwise. I assessed her again at four-six weeks when she had completed her post-surgical eye drops and was able to remain drop-free.

Mrs NA's IOP remained in the 14-15 range without drops in her right eye. She was grateful for her optometrist's initiative and his understanding of MIGS devices as an option for her management, leading up to her referral to see me.

The collaborative team management of Mrs NA ensured that she was able to make the most informed decision for her combined cataract and glaucoma surgery, with an optimised outcome for her in the context of the available options.

Discussion

The development of MIGS devices spans over a decade, and was originally born out of a desire to provide gentler alternatives to penetrating glaucoma surgery, without the inherent risks and ongoing management issues.

Treatment options before MIGS

Options which have been available to us, with variable efficacy, include:

Eye drops. Prostaglandin analogues, beta blockers, alpha-agonists, and Carbonic anhydrase inhibitors (while miotics are very infrequently used now).

Laser therapies. Laser trabeculoplasty (Argon/ALT mostly superseded now by Selective/SLT).

Ciliary body ablative procedures. Cyclodiode, endoscopic cyclo-ablation.

Figure 2. Trans-trabecular devices: Stent and iStent inject (Glaukos)

Penetrating surgeries. Trabeculectomy and drainage tubes.

MIGs devices

In developing these less invasive devices, the 'ideal' therapy would be considered as being safe, predictable, efficacious, titratable and complication-free. They would also be free of requiring patient compliance, and quietly work away in the background. Realistically however, this doesn't exist. Nevertheless, setting these goals have been important in the development MIGS devices.

The following is an overview of some of the more commonly available devices, with a summary of their key features.

Trans-Trabecular devices: Stent and iStent inject (Glaukos)

Effectiveness depends on the targeted placement into areas of optimal aqueous outflow. The device, which consists of an inert titanium material coated with an anticoagulant, is inserted directly into the trabecular meshwork, secured by a collar (Figure 2). It is safe in current MRI and x-ray devices.

Intra-canalicular devices: Hydrus (Ivantus)

Less reliant on targeted placement, as the broader placement of the device along the trabecular meshwork improves its chances of corresponding to collector channels and aqueous veins (Figure 3).

Supraciliary devices: Cypass (Alcon)

Initially, these devices showed promise as a novel and effective means of

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Figure 3. Intra-canalicular devices: Hydrus (Ivantus).

Drop toxicity and at-risk ocular surfaces

Managing ocular surface disease for a lifetime of glaucoma

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One of the most common complaints we all hear from patients we manage with glaucoma is that of sore, uncomfortable, red eyes. A structured approach to diagnosis and management, as well as a raft of new treatment options can make this a much more satisfactory condition to manage. Ocular surface disease (OSD) is often multifactorial. When I approach a patient with symptoms of OSD, I like to focus on key features of the examination that help me categorise the cause of the OSD and then think about treatments that either help treat the OSD, or if glaucoma drops are implicated, what alternative treatments may work for the patient.

Examination

There are a few features of the examination that really help classify OSD and are commonly missed or under-appreciated. I pay particular attention to the lid margin. Is there meibomian gland dysfunction? If so, I like to ask about a history of rosacea as this often co-exists and helps guide my treatment approach. I treat all but the most minor meibomian gland dysfunction with hot compresses and if it is moderate-to-severe or associated with rosacea, I have a low threshold for giving a course of low-dose tetracycline, such as doxycycline. I also specifically look for other lid margin changes like keratinisation (Figure 1), which is often missed and requires a tailored management strategy. This may sometimes require the use of therapeutic contact lenses or surgery.

Next, I assess the conjunctiva, and while doing so I know that by the time I see conjunctival signs of OSD there has already been significant goblet cell loss and aggressive treatment is probably needed. I look for injection and increased vascularity, including routinely flipping the lids to look for papillae, follicles, exposed concretions, fibrosis or symblepharon.

I am careful how I stain the eye to give a clear picture of how the ocular surface is functioning. I always use a small amount of fluorescein from a strip reconstituted with normal saline (not local anaesthetic), because when assessing the tear film, I want to see how it functions normally for this patient. I tend to only perform Schirmer's strip tests in patients with whom I am concerned about aqueous deficiency. In these cases, I do use local anaesthetic as well as repeating the measurement at a subsequent visit before trying to interpret the result. I pay particular attention to the limbal architecture, looking for areas of encroachment of the conjunctiva onto the cornea, which suggests localised loss of limbal barrier function. I also look for whorl keratopathy (Figure 2) or very fine generalised staining to suggest generalised limbal stem cell deficiency. These are important because limbal stem cell failure (Figure 3) is a blinding condition.

Treatment options

Once I've fully examined the patient, I try to synthesise the findings to guide two major decision points: 1) what are the contributors to OSD that I can address, and 2) how severe is the OSD. This helps guide how aggressive I need

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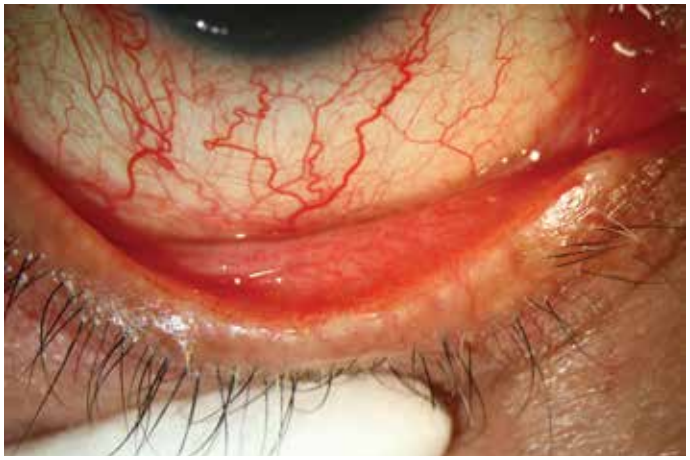

Figure 1. Lids of the patient show lid margin keratinisation with posterior migration of the cutaneo-conjunctival boundary and build up of keratin. Also severe meibomian gland dysfunction.

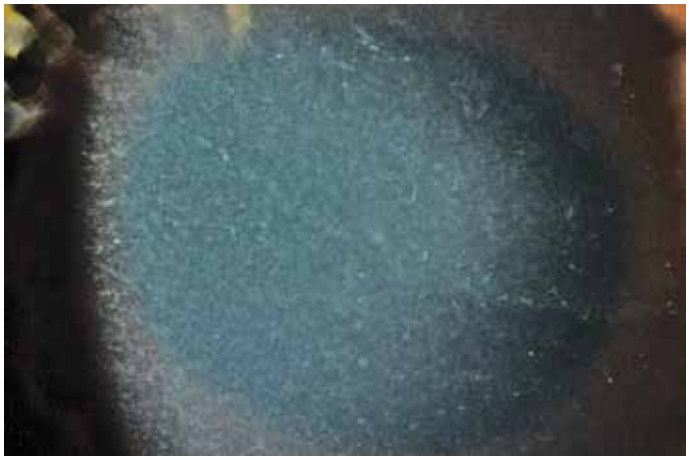

Figure 2. Mild whorl keratopathy from limbal stem cell toxicity following 2x 5-fluorouracil injections after a trabeculectomy

Drop toxicity

From page 7

to be (Figure 3). I think an assessment of the severity is useful because in glaucoma we are often faced with the challenge of having to balance the need to continue an effective treatment regime versus worsening the OSD.

We all know that the load of topical preservatives contained within anti-glaucoma drops contributes to ocular surface disease, but I am still amazed at the number of patients using frequent ocular lubricants with preservatives.

My first step in management is to change patients to preservative-free lubricants. I then look to see if any of their topical medications have preservative-free alternatives (Table 1). Thankfully the number of preservative-free glaucoma agents is slowly growing, with a few combination agents coming onto the market as well.

Class	Active ingredient	Brand name
Prostaglandin analogues	Tafluprost 0.015%	Saflutan
	Bimatoprost 0.03%	Lumigan PF
Beta-blockers	Timolol 0.25 or 0.5%	Timoptic in Ocudose*
Parasympathomemitics	Pilocarpine 2%	Pilocarpine minims*
Combinations	Bimatoprost 0.03% & Timolol 0.5%	Ganfort PF
	Dorzolamide 2% & Timolol 0.5%	Cosopt PF*

*Not available on the PBS

Table 1. Preservative-free topical medications

Unfortunately, even the preservative-free glaucoma medications can still contribute to OSD. I think angle-based laser treatments are much underused and offer a great alternative for many people suffering from side effects of topical medication. Selective laser trabeculoplasty (SLT) has a well-established role in glaucoma treatment, and recently a new alternative called micropulse laser trabeculoplasty (MLT) is proving to be another useful option.[1]

As pointed out in this issue of *Pharma*, there has been growing enthusiasm for a number of small implantable devices for lowing IOP. Although they are quite heterogeneous in their surgical approach and who they are suitable for, they have all been grouped under the heading 'Minimally Invasive Glaucoma Surgery' (MIGS). For those patients who are undergoing surgery anyway, these devices offer the potential for reduced dependence on glaucoma drops with a minimal increase in surgical risk.

Another possible option currently undergoing clinical trials are intraocular, injectable, ultra-low dose deposits of prostaglandin analogues. If proven safe and effective, they may provide an excellent way to achieve medical IOP lowering without topical side effects.

Lastly, I like to think about how I can alter the chemical milieu on the ocular surface to the patients' advantage. Lubricants may help to lower ocular surface osmolarity, but do little to address inflammation, which we know is a significant contributor to disease in OSD.

I am particularly careful in my approach to managing inflammation in glaucoma patients because of the attendant risks of steroid responsive glaucoma in these patients. In cases where glaucoma is mild or there is the ability to manage a potential pressure rise, I think it is reasonable to use fluorometholone drops (FML, Allergan Australia Pty Ltd) once to twice per day. It is potent on the ocular surface with a relatively lower risk of IOP rise.

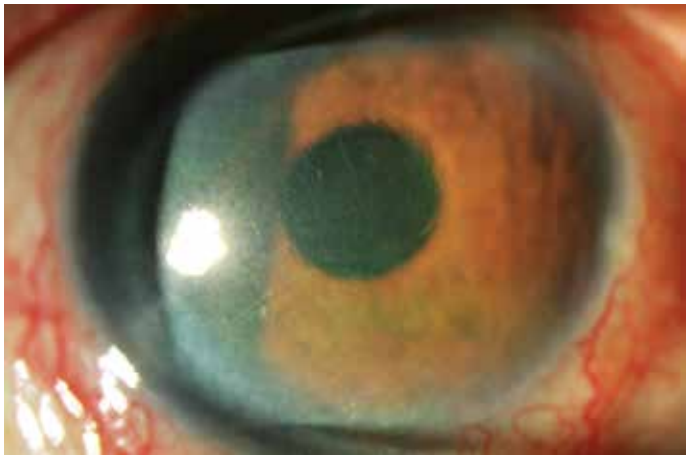

Figure 3. Severe corneal epitheliopathy and partial limbal stem cell failure following multiple glaucoma operations and topical treatments

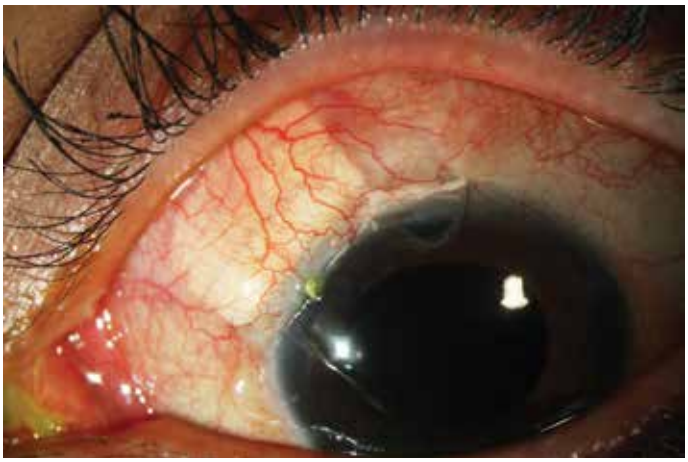

Figure 4. Ocular surface disease with previous Baerveldt tube. Note severe conjunctival hyperaemia, conjunctival and tenons thinning and loss of shiny smooth surface. Mild to moderate meibomian gland dys-function. There is also a protruding suture end with mucous plugging.

If the patient has a known history of steroid response, or is at high risk of progression if a pressure rise occurs, I advocate the use of topical low dose cyclosporin.*

Other options in our armamentarium include N-acetylcysteine and serum tears, (neither of which can be prescribed by Australian optometrists).

N-acetylcysteine is a mucolytic and matrix metaloproteinase inhibitor. It has properties that improve corneal wetting, break down mucous and filaments and prevent corneal melting. (N-acetylcysteine is only available compounded in a 10% concentration).

Serum tears are made from the patient's own blood which is spun down and the serum component manufactured into an eye drop. It has anti-inflammatory properties and cytokines that promote cell growth.

The range of options for patients with sore, burning eyes after years of glaucoma treatment is improving steadily. Attention to often-missed clinical features will yield specific conditions to which targeted treatment can be applied.

Management of OSD always begins by remembering the basics: use of preservative-free lubricants and treating lid disease. An awareness of the widening availability of options including laser, surgery, and novel forms of medications are giving clinicians much greater mastery over this condition.

* In Australia, ophthalmic cyclosporine has not been approved by the Therapeutic Goods Administration (TGA). However, it can be accessed by patients in Australia through the Special Access Scheme, and resources are available for practitioners seeking to prescribe the formulation.

1. Abramowitz B et al. Selective laser trabeculoplasty vs micropulse laser trabeculoplasty in open-angle glaucoma. *Clin Ophthalmol* 2018; 12: 1599-1604.

MIGS

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lowering IOP by introduction along the supraciliary space between the ciliary body and sclera internally, which was demonstrated favourably in the COMPASS trial.[1] While they were shown to be effective in lowering the IOP, the recently available five-year data on the extension study revealed that the device was associated with increased endothelial cell loss when combined with cataract surgery, compared to cataract surgery alone (20.5 per cent vs 10.1 per cent at five years).[1] As a result, this device was voluntarily and responsibly withdrawn from the market on 29 August 2018, and is no longer available (Figure 4).

Figure 4. Supraciliary devices: Cypass (Alcon).

Subconjunctival devices: Xen Gel Stent (Allergan)

As MIGS devices become more creative and potentially more invasive, we start to see blurring of the lines defining 'minimally' invasive surgery. This could make room for another class of devices dubbed 'moderately' invasive glaucoma surgery ('MOGS' perhaps?).

The main currently-available device in Australia is the Xen Gel stent device. The Xen implant is ideally suited to patients with uncomplicated open angle, pseudoexfoliative, or pigmentary glaucoma, who have healthy conjunctiva and can manage the post-operative care which includes bleb management. It is indicated in patients with moderate-to-advanced uncontrolled glaucoma unresponsive to maximum tolerated medical therapy (Figure 5).

Ultimately, each drainage device comes with its own learning curve, and paramount to all drainage devices is the requirement for optimal visualisation of the anterior chamber angle.

In relation to MIGS devices, as a general rule, the more invasive the procedure, the more effective it will be. For example: trans-trabecular devices such as iStent inject have a very good safety profile and low risk of complications, albeit with a relatively modest pressure-lowering effect when compared to trabeculectomy. In comparison, subconjunctival procedures such as Xen Gel stent can have a more dramatic pressure lowering effect, but they come with a higher risk of potential morbidity, including risks of infections, greater risk of hypotony and the patient engagement required in bleb management and subconjunctival anti-scarring injections.

1. Two-Year COMPASS Trial Results: Supraciliary Microstenting with Phacoemulsification in Patients with Open-Angle Glaucoma and Cataracts Vold, Steven et al. *Ophthalmology* 2016; 127: 2103-2112.

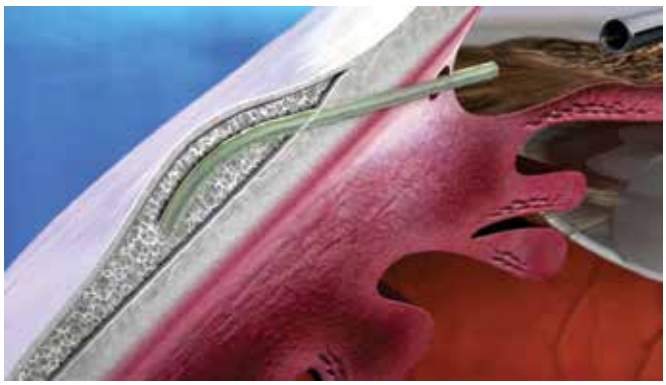

Figure 5. Subconjunctival devices: Xen Gel Stent (Allergan)

Confessions of a clinician

Tips for managing AMD

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Age-related macular degeneration (AMD) is the leading cause of vision loss and blindness in Australia. One in four cases of AMD are classified as normal by eye care professionals.[1] Poor visual acuity at presentation translates to poor outcomes and up to 87 per cent of patients with neovascular AMD have a visual acuity worse than 6/12 at the time of diagnosis.[2,3] Additionally, one in five patients that need treatment may be lost to follow-up.[4]

These statistics paint a sobering picture on the state of AMD care in Australia and worldwide. In this article, I describe a series of clinical strategies to supercharge the way you diagnose, understand and manage AMD.

CONFESSION 1. THE RULES KEEP CHANGING

Solution: Clinical practice guidelines

There is a plethora of resources now available to practising clinicians aimed at improving clinical practice patterns and ultimately, patient outcomes. Broadly, these resources include convenient and easily-accessible forms of information, such as case studies, peer-reviewed publications, chair-side references and clinical guidelines (Table 1).[5]

Optometry Australia has recently developed a clinical practice guide, providing evidence-based information about current best practice in the diagnosis, treatment and management of age-related macular degeneration. This is an open-access resource available on the Optometry Australia website.

Because the collective wisdom is constantly evolving, these tools can be helpful for distinguishing fact from fiction and often provide all of the relevant information succinctly, filtered through the lens of an expert committee. Although the evidence for efficacy of these materials is limited and the best approach for optimising their efficacy still requires clarification, they are indeed one of the few methods we have of translating research findings into clinical practice. They help to define and promote the use of evidence-based procedures of proven benefit and discourage ineffective alternatives.

In these materials, you can find ready support on a myriad of topics ranging from general management advice, diagnosis, procedures, referrals, test ordering, patient education, clinical prevention and professional-patient communication. They may be accessible through one or multiple means (either personally, online, through mass mailing and most commonly, via publication in a peer-reviewed journal) and result in a statistically significant improvement in professional practice.[5]

CONFESSION 2. I AM NOT CONFIDENT ABOUT WHAT I'M SEEING

Solution: Clinical decision support platforms

Today's 'routine' eye examination is incredibly complex. In AMD alone, we may be accustomed to performing a targeted history, a routine battery of entrance tests, followed by fundoscopy and retinal photography. It helps to know which instrument to use and when. Optical coherence tomography (OCT) is quickly becoming the norm[6] and OCT angiography, fundus autofluorescence and other imaging techniques, including near infrared imaging or ultra-widefield imaging, are also effective.[7,8] The combination of multiple modalities improves the diagnosis of ocular disease but may not always be accessible and is often time consuming and subject to interpretation.

Take for instance, a routine 512 x 128 macular OCT volume scan acquired using the Cirrus HD-OCT (Carl Zeiss Meditec). This means that in addition to the rest of the examination, the

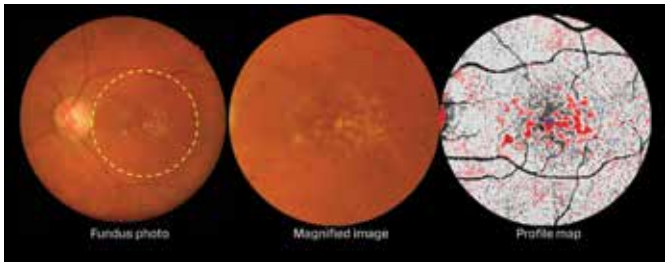

Figure 1. A clinical decision support tool currently in development at Centre for Eye Health. This method uses unsupervised cluster analysis to semi-automatically classify drusen (red) and pigmentary abnormalities (blue). Each distinct colour in the profile map corresponds to a statistically separable, specific anatomic structure.

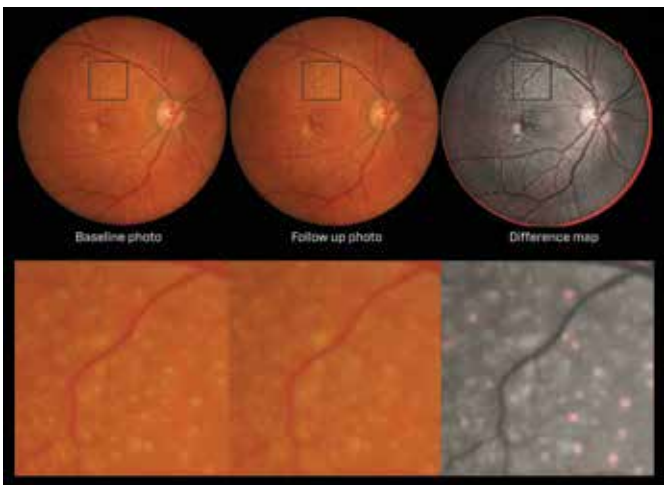

Figure 2. Case images taken 16 months apart from an eye with intermediate AMD. The change or difference map pictured on the right alerts the clinician to areas of drusen regression (red).

optometrist has an added duty of care to review each of the 128 serial line scans taken per eye, meaning a total of 256 B-scans per patient. Add to this the myriad of prognostic biomarkers, which are relevant to stratifying risk of AMD progression[9] and the complexity is mind-boggling.

Support for accurately interpreting imaging results is on its way. With the aid of computational approaches and machine learning, we can expect to see a growing suite of clinical decision-making support tools. Risk calculators represent an example many will be more familiar with, which is commonly applied to case history data.

Figures 1 and 2 showcase two computational methods of analysing AMD-related ocular imaging data in development at the Centre for Eye Health.[10,11] Current commercially-available software on the Cirrus HD-OCT, described as 'advanced retinal pigment epithelium (RPE) analysis,' presents a similar tool with the capacity to automatically quantify drusen load.

Guideline title	Produced by	Year
Clinical practice guide for the diagnosis, treatment and management of age-related macular degeneration	Optometry Australia	2019 (New)
Age-related macular degeneration NICE guideline	National Institute for Health and Care Excellence	2018
BMJ Best Practice Age-related macular degeneration	British Medical Journal	2018
Referral pathway for AMD screening and management by optometrists	The Royal Australian and New Zealand College of Ophthalmologists	2018
NZ National guidelines – management of neovascular AMD	New Zealand Association of Optometrists	2018
Practical guidelines for the treatment of AMD	Review of Optometry	2017
Age-related macular degeneration preferred practice pattern	American Academy of Ophthalmology	2015
Guidelines for the collaborative management of persons with age-related macular degeneration by health- and eye-care professionals	Canadian Journal of Optometry	2015
Age-related macular degeneration: Guidelines for management	Royal College of Ophthalmologists	2013
Treatment of age-related macular degeneration	Australian Prescriber	2012
AMD – advice to optometrists	Optical Confederation	2010
Age-related macular degeneration (management recommendations)	International Council of Ophthalmology	2007
Care of the patent with age-related macular degeneration	American Optometric Association	2004

Table 1. Clinical practice guidelines on AMD, last updated January 2019

CONFESSION 3. MY PATIENTS REFUSE TO QUIT SMOKING

Solution: Motivational interviewing and printed patient educational materials

Having fulfilled the onerous task of keeping up-to-date with the latest evidence, acquiring and correctly interpreting the sum of results from the eye examination, it can be tempting to presume that our job is done; however, all that work may be in vain if not disseminated to the patient. Several risk factors carry a well-described association with the onset and progression of AMD, such as age, family history and smoking. Hypertension, cardiovascular disease, raised BMI, poor diet and lack of exercise are less often considered but represent additional and more importantly, modifiable risk factors for disease. Therefore, your AMD management strategy should regularly include advice on improving dietary habits as well as the benefits of nutritional supplements and quitting or reducing smoking.

As optometrists, our unique position in the health care system empowers us to educate and reinforce key management strategies that can make a difference and ultimately, save sight. Behaviour change in chronic disease can be difficult, particularly in asymptomatic cases where the fear of change, ambivalence, lack of skills or a history of prior failures abound; however, it can also be one of the most rewarding aspects of routine optometric practice and a real relationship-builder between you and your patients.

I encourage you to have those 'difficult' conversations. But be advised that authoritarian, confrontational or guilt-

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Managing AMD

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inducing communications are often counter-productive. If you're finding it hard to know where to start, motivational interviewing describes an evidence-based, directive counselling approach to behaviour change. I urge all practitioners to learn more about its application in chronic diseases.[12] Personalising the message to the individual is important and relevant material or contact from patient support groups, such as the Macular Disease Foundation Australia, or low vision services, including Guide Dogs Australia or Vision Australia, can also be invaluable.

Optometry has entered a period with an ever-increasing range of tools and information to supercharge the way we manage AMD and other diseases. With this comes both challenges and opportunities to apply strategies for the benefit of our patients. How will you improve the way you manage AMD tomorrow?

Conflicts of interest: The author is a named inventor on a provisional patent relating to the use of pattern recognition on ocular imaging data. Centre for Eye Health is an initiative of Guide Dogs NSW/ACT and UNSW Sydney and has an affiliation with the Macular Disease Foundation Australia.

Acknowledgements: The author thanks Michael Yapp and Professor Michael Kalloniatis for reviewing the manuscript.

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GUIDE

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Glaucoma management for optometrists in 2019

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Are the NHMRC guidelines still useful?

Glaucoma is one of the leading causes of irreversible blindness around the world. Aside from its expected increase in prevalence due to an ageing population,[1] another issue surrounding the disease is the problem of underdiagnosis[2,3] or late diagnosis.[4]

Currently, the National Health and Medical Research Council (NHMRC) glaucoma guidelines present a summary of evidence to guide clinical practice in Australia.[5] However, given the age of these guidelines (nearing 10 years old), it is important to consider more recent evidence and research to inform best practice in the current clinical climate. The NHMRC guidelines were also written prior to recent changes to professional recommendations and registration standards for optometric management of glaucoma by the Optometry Board of Australia, Optometry Australia and the Royal Australian and New Zealand College of Ophthalmologists.[6-8]

Through the presentation of a recent case managed at the Centre for Eye Health (CFEH), I will reinforce the thought processes that are critical for glaucoma management, and how these relate to the most current NHMRC guidelines published in 2010. I encourage you to think about workflow and how the management plan evolved over a number of follow-up visits. Finally, I will present some more recent ideas in the field of glaucoma and how patient management will continue to change in the future.

CASE REPORT

A 60-year-old Caucasian female was referred to the CFEH Glaucoma Management Clinic – a glaucoma clinic staffed by CFEH optometrists working in collaboration with ophthalmologists from the local health district. She had a family history of glaucoma (mother, with apparent severe vision loss). She had previously seen an ophthalmologist for laser peripheral iridotomy and received an initial prescription of latanoprost (Xalatan) in 2013, but had since stopped it on her own. Her entrance test findings are summarised below (Table 1).

Dilated fundus examination showed medium-sized discs with deep cups in both eyes. The right neuroretinal rim and retinal nerve fibre layer (RNFL) were intact, but the left rim had a notch at around 5 o'clock and a corresponding wedge defect of the adjacent RNFL (Figure 1A).

There was also a disc haemorrhage at 12 o'clock in the left eye, with a thinner slit of RNFL defect at around 12:30 o'clock (Figure 1A). Optical coherence tomography (OCT) showed a concordant result (Figure 1B). The left visual field results showed no correlating glaucomatous defect on the pattern deviation map: only isolated points of reduction around the seeding points (Figure 1C). The field result flagged some of the global indices as abnormal, but this failed to meet typical glaucomatous field loss criteria.

What is your diagnosis?

An evolving definition of glaucoma diagnosis

Glaucoma was previously thought to be a 'pressure-related' optic neuropathy. As time went by, the definition of the disease changed to one that included changes at the optic nerve head and visual field. Later still, the complexity of glaucoma has

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	OD	OS
Refraction and visual acuity	+3.50/-1.00x75 (6/6)	+5.00DS (6/6)
Intraocular pressures (IOP)	12 mmHg	13 mmHg
Central corneal thicknesses	525 microns	514 microns
Gonioscopy	Scleral spur superiorly and inferiorly; pigmented trabecular meshwork nasally and temporally	Scleral spur superiorly, nasally and temporally, and pigmented trabecular meshwork inferiorly
Slitlamp examination	Iridotomy patent superiorly No other secondary risk factors for glaucoma	Iridotomy patent superiorly No other secondary risk factors for glaucoma

Table 1. Patient's entrance test findings

IOP Medications available in Australia

IOP drops are the optometrists' first-line treatment for glaucoma patients. [1,2] medications, potential side effects and contraindications.

Preparations by Class		Mechanism of action	Efficacy	Order of treatment choices
	**Prostaglandin analogues** • Latanoprost 0.005% (Brand name: Xalatan) • Travoprost 0.004% (Brand name: Travatan) • Bimatoprost 0.03% (Brand name: Lumigan*) • Tafluprost 0.0015% (Brand name: Saflutan*)	Increase aqueous outflow	**25-35%** Maximum effect: 8-12 hours	First
	**Beta-blockers** **Non-selective agents:** • Timolol 0.25%, 0.5%, 1% (Brand name: Timoptol, Nyogel, Timoptic*) **Selective agents:** • Betaxolol 0.25%, 0.5% (Brand name: Betoptic)	Decrease aqueous production	**20-25%** Maximum effect: 2 hours	First
	**Alpha2-agonists** • Brimonidine 0.2%, 0.15% (Brand name: Alphagan) • Apraclonidine† 0.5% (Brand name: Iopidine)	Increase aqueous outflow and decrease aqueous production	**10-25%** Maximum effect: 1-4 hours	Second
	**Carbonic anhydrase inhibitors** Topical: • Dorzolamide 2% (Brand name: Trusopt) • Brinzolamide 1% (Brand name: Azopt)	Decrease aqueous production	**15-25%** Maximum effect: 2 hours	Second
	**Cholinergics (miotics)** • Pilocarpine 1%, 2% (Brand name: Isopto Carpine, Pilocarpine minims*†)	Increase aqueous outflow	**15-20%** Maximum effect: 3-4 hours	Third
	**Combination therapies‡** • Brimonidine 0.2%/timolol 0.5% (Brand name: Combigan) • Dorzolamide 2%/timolol 0.5% (Brand name: Cosopt*) • Travoprost 0.004%/timolol 0.5% (Brand name: DuoTrav) • Latanoprost 0.005%/timolol 0.5% (Brand name: Xalacom) • Bimatoprost 0.03%/timolol 0.5% (Brand name: Ganfort*) • Brinzolamide 1%/timolol 0.5% (Brand name: Azarga) • Brinzolamide 1%/brimonidine 0.2% (Brand name: Simbrinza)	As for individual components	**20-35%**	Second

*Preservative-free option
†Currently not available on the PBS
‡Restrictive benefit: the condition must have been inadequately controlled with monotherapy.

for the management of glaucoma

It is imperative that all practicing optometrists are aware of the IOP

Optometry AUSTRALIA

	Daily dosage	Ocular side effects	Systemic side effects	Contraindications
	Once daily (night)	• Increase in iris pigmentation • Darkening, thickening & lengthening of eyelashes • Conjunctival hyperaemia • Periorbital pigmentation	• Uncommon - may cause respiratory symptoms in susceptible individuals	No contraindications **Precautions:** • Intraocular inflammation (iritis, uveitis) • History of herpetic keratitis • Aphakia or pseudophakia (potential for macular oedema)
	One to two times daily	• Transient ocular discomfort • Blurred vision • Increased lacrimation • Foreign body (FB) sensation	• Headache • Bradycardia • Decreased libido • Bronchospasm • Nausea	• Sinus bradycardia • Overt cardiac failure history • Cardiogenic shock **Precautions:** • Asthma • Severe chronic obstructive pulmonary disease (COPD) (selective agents, i.e. betaxolol preferred)
	Two to three times daily	• Common - Allergic reactions • Hyperaemia • Burning/stinging • Foreign body (FB) sensation • Blurring	• Dry mouth • Headache • Fatigue	Patients receiving MAOIs **Precautions:** • Severe cardiovascular disease • May have loss of effect over time
	Two to three times daily	• Allergic reactions • Burning/stinging	• Headache • Bitter taste • Dry mouth • Nausea • Fatigue	• Allergy to sulfonamides • Severe renal impairment **Precautions:** • Corneal grafts • Endothelial dystrophy (may cause corneal oedema)
	Three to four times daily	• Eye ache/pain • Blurred vision • Myopic shift • Miosis • Retinal detachment (rare)	• Headache • Nausea • Dizziness	• Uveitis/Iritis • Secondary glaucoma
	Combigan: Twice daily Cosopt: Twice daily DuoTrav: Once daily Xalacom: Once daily Ganfort: Once daily Azarga: Twice daily Simbrinza: Twice daily	As for individual components		As for individual components

1. NHMRC. Guidelines for the Screening, Prognosis, Diagnosis, Management and Prevention of Glaucoma. Canberra, Australia; 2010.

2. MIMS Online [Internet]. Medical Information Management System. [cited 2018 December 12]. Available from https://www.mimsonline.com.au.

Management

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become recognised, and now its formal definition includes a constellation of possible signs,[9,10] with an emphasis on its multifactorial aetiology.[11]

What is interesting about more modern definitions of glaucoma is that visual field defects do not need to be present.

Pre-perimetric glaucoma is not a new concept, having been recognised in the literature as early as the 1970s.[12] However, the NHMRC guidelines do not consider a diagnosis of pre-perimetric glaucoma. Indeed, a mild stage of glaucoma reportedly should still have a glaucomatous visual field defect. In contrast, more recent clinical guidelines such as the American Academy of Ophthalmology suggest that the earliest stages of glaucoma may not have a visual field defect revealed using standard automated perimetry.[13]

Does our patient have glaucoma? Several structural features of glaucoma are present: enlarged and asymmetric cup in the left eye compared to the right, the presence of a contiguous RNFL defect, and the presence of a disc haemorrhage. Her risk profile is also noteworthy: age and positive first degree relative with glaucoma are both considered to be high risk factors.

On the weight of this evidence, despite the lack of correlating functional loss, this patient has been diagnosed with *left pre-perimetric low tension glaucoma*. Now that she has received a diagnosis of glaucoma, consider the following question:

Does this patient require treatment?

Clarity in diagnosis, clarity in treatment: evidence-based practice

The stage of glaucoma is important for titrating treatment. Although a target intra-ocular pressure (IOP) reduction of 25-30 per cent is typically indicated for most patients, consider the evidence provided in clinical trials with respect to the stage of glaucoma.

The Early Manifest Glaucoma Trial had a mean IOP reduction of 25 per cent to reduce the rate of progression.[14] The Collaborative Initial Glaucoma Treatment Study, on the other hand, aimed to reduce the IOP by at least 30 per cent using whatever means possible, however, this study notably included a range of patients with different stages of glaucoma.[15]

The Advanced Glaucoma Intervention Study[16] may be a bit of a misnomer: it simply referred to patients who had visual field loss with inadequate IOP reduction when on maximum medical therapy. This study showed that patients achieving a mean IOP of < 14 mmHg were more stable than patients with IOP > 17.5 mmHg. Patients in whom IOP control was more stable (< 18 mmHg at 100 per cent of all visits) were also more stable than patients with fluctuating IOP. Although not clearly stated in the study, the percentage reduction inferred from the baseline characteristics of the patients was approximately 40 per cent in the most stable group, and 31.3 per cent in a less stable group.

But what about patients without visual field loss? Is it worth it to initiate treatment that may affect quality of life in a patient with no apparent functional impairment? More recent clinical studies have examined the role of treatment in patients with pre-perimetric glaucoma.[17-19] These have suggested that an IOP reduction of at least 20 per cent was associated with a slower rate of progression.

What do the outcomes of these trials suggest? It appears that patients with an earlier stage of glaucoma may require less aggressive treatment compared to patients with late stage disease. They also suggest that stability of IOP (less variation within a day and between visits) is important, reinforcing the notion of compliance and regular follow-up appointments.

Therefore, my next question is:

What is/are the best treatment options for this patient?

Given the propensity for excellent IOP reduction (approximately 30 per cent, which generally meets the IOP target as monotherapy), prostaglandin analogues are generally considered to be first-line treatment.[20] However, first-line selective laser trabeculoplasty (SLT) should also be considered. Although SLT is arguably less predictable in terms of IOP reduction in comparison to topical medications,[21] it is a useful alternative as a drop-sparing therapy and to mitigate issues with compliance and potential ongoing cost.[22]

Several studies have shown that IOP reduction comparable to prostaglandin analogues can be achieved with SLT up to 12 months from the procedure.[23]

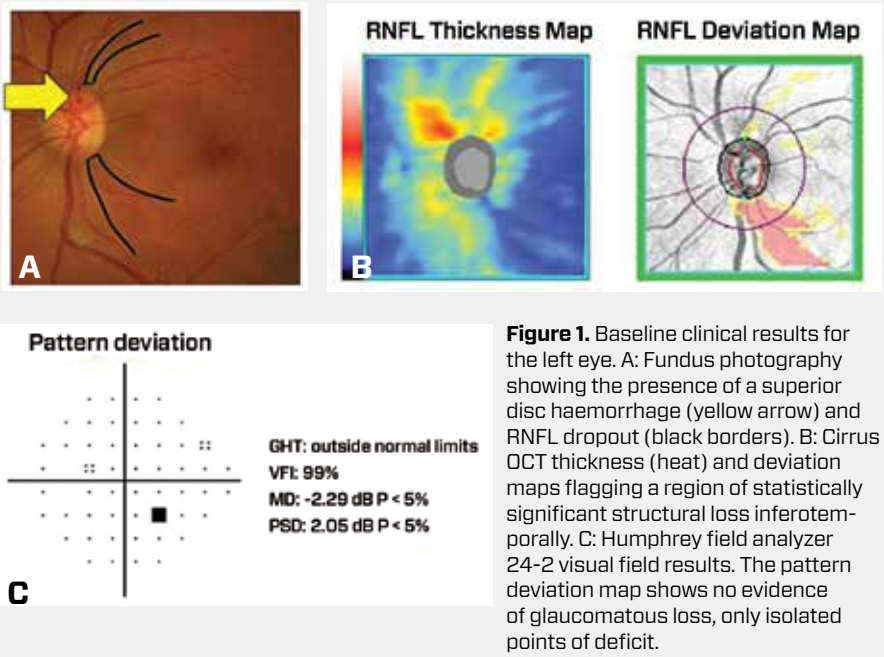

Figure 1. Baseline clinical results for the left eye. A: Fundus photography showing the presence of a superior disc haemorrhage (yellow arrow) and RNFL dropout (black borders). B: Cirrus OCT thickness (heat) and deviation maps flagging a region of statistically significant structural loss inferotemporally. C: Humphrey field analyzer 24-2 visual field results. The pattern deviation map shows no evidence of glaucomatous loss, only isolated points of deficit.

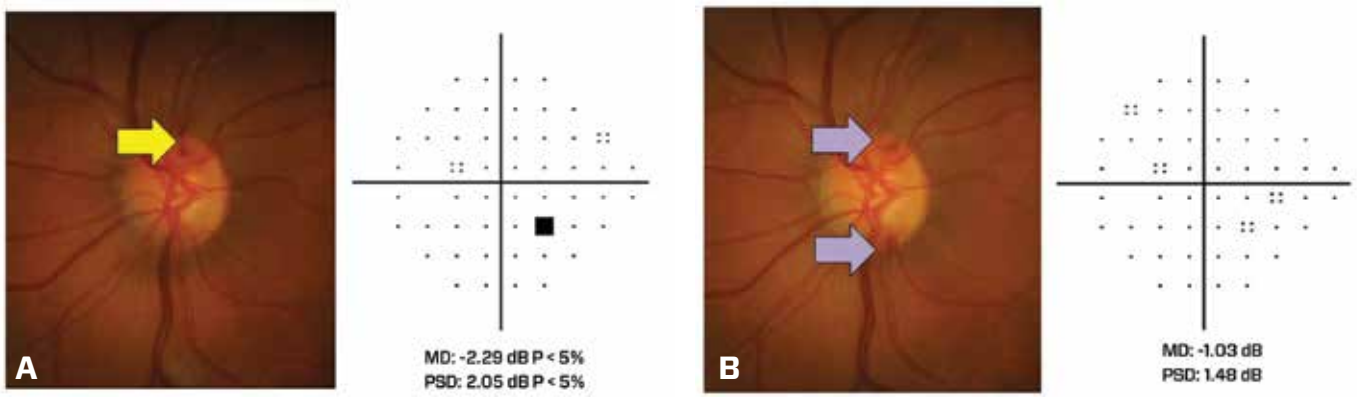

Figure 2. Comparison of A: baseline and B: follow-up fundus photographs, visual field pattern deviation maps and visual field global indices (mean deviation and pattern standard deviation). There is a recurrent disc haemorrhage superiorly and a new disc haemorrhage inferiorly at the follow-up visit. However, there was no worsening of the visual field result.

However, the effect of IOP reduction appears to diminish over time, with one study suggesting that only 11-31 per cent of patients still have a reduction of > 20 per cent at five years.[24] One of the advantages of SLT is that it can be repeated later, with similar efficacy compared to the initial procedure. Although it is difficult to predict which patient will successfully respond to SLT, factors such as higher baseline IOP and a more heavily pigmented trabecular meshwork have been suggested to play a role.

Case: Follow-up 1

Treatment options including topical medications or SLT were discussed. Six weeks after initiating treatment with latanoprost 0.005% (Xalatan) nightly to the left eye only, the patient's IOP had reduced to 10 mmHg (approximately 30 per cent reduction). This was satisfactory and on target, and so a follow-up appointment with repeat assessment was made for six months from initial baseline.

Question:

What other tests may be useful for this patient?

High-tension, low-tension, secondary glaucoma – are they different?

Several clinical trials distinguish between high-tension (primary open angle glaucoma) and normal or low-tension glaucoma.[14,25] Although there are some slight differences in the IOP targets for each subtype of glaucoma, are they really that different? Most of the time, a five per cent difference in IOP (that is, from 25 per cent to 30 per cent reduction) could be negligible and would be relevant in cases of higher baseline IOP; a baseline pressure of 15 mmHg means this five per cent is < 1 mmHg, while a baseline of 22 mmHg would mean just over 1 mmHg. Though the Early Manifest Glaucoma Trial suggested that every 1 mmHg reduction from baseline meant a 10 per cent decrease in risk of progression, we should bear in mind the potential natural measurement variability of approximately 2–3 mmHg.

The reason for distinguishing the different types of glaucoma is primarily due to their progression rate. The Early Manifest Glaucoma Trial showed that patients with untreated pseudoexfoliative glaucoma tend to progress much faster compared to high-tension glaucoma, and that low-tension glaucoma patients tend to progress the slowest.[14,26] Morphological studies of the optic nerve have suggested a greater extent of damage in high-tension compared to low-tension glaucoma.[27] Paradoxically though, visual field defects in low-tension glaucoma are suggested to be more localised.[28] The theory that the paracentral area is affected more in low-tension glaucoma has been debated,[29, 30] but clinicians should remain wary regarding this visual field location.

We need to understand the distinction between glaucoma types to provide a reasonable prognosis for the patient and put this into perspective with the chosen treatment regimen. In light of these potential differences, a 10-2 visual field test may be useful in some cases to examine for subtle central losses not revealed by the 24-2 or 30-2.[31, 32] Again, there are no clear recommendations regarding the frequency or alternation of these tests. Although some studies have expounded on the benefits of the 10-2, it is equally important to remember that these are complementary to the 24-2, and will miss an almost equal number of field defects if performed in isolation.[33]

The NHMRC guidelines provide recommendations for the number of visual fields tests to detect functional progression. This is dependent upon the variability of the patient and the expected progression rate. It would not be uncommon to find that more than two tests per year—that is, more than the current rebated number for optometrists—are required to detect functional progression in some glaucoma patients.[34] More recently, a study[35] has suggested that frontloading and clustering visual fields tests may be informative. Performing three fields at baseline and at follow-up, rather than spacing each individual test at even intervals, may be beneficial in detecting change over time.

Further to additional visual field testing, other measurements of IOP may be tailored to the individual case. IOP phasing has been shown to identify the different peaks of IOP throughout the day, which may differ across patients.[36] The water drinking test may also reveal some patients with

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sustained high IOP when placed under conditions of osmotic stress.[37]

Case: Follow-up 2

The patient presented for a follow-up appointment six months from her baseline visit. Her intraocular pressures remained reduced and on target at 10 mmHg OS (the untreated right eye remained at 14 mmHg). She reported no adverse effects to the prescribed medication. The OCT showed no change, and the visual field results for the left eye showed fewer points flagged on the pattern deviation map (Figure 2). However, there were two disc haemorrhages, one of which was recurrent at the same location as the baseline visit (Figure 2).

What is the significance of this sign and is there any change to the management?

Risk factors for progression: beware the bleeds

Though a number of risk factors have often been cited, two specific aspects of the clinical examination remain almost ubiquitous in their appearance: elevated IOP and the presence of a disc haemorrhage.[17-19] By definition, a disc haemorrhage associated with glaucoma needs to meet the following criteria, as opposed to other causes of bleeding:[38]

- Proximity: within 1 disc diameter of the disc margin

- Linearity: appears linear and perpendicular to the disc margin

- Depth: appears superficial within the prelaminar region

- Length: typically extending from rim to the peripapillary area

After resolution of the disc haemorrhage in about 6–8 weeks, like any other ischaemic event in the eye, it is not uncommon to find a newly formed area of RNFL dropout.[39,40] It is therefore critical to review these patients within 3–4 months of documenting a haemorrhage to obtain further structural and functional measurements of the eye when the loss is more pronounced.[41]

It is important to note that a recurrent disc haemorrhage is often a sign of uncontrolled disease or progression. However, not all recurrences are equal. Once a patient has had a disc haemorrhage at a particular location, and if structural loss has already reached the point of the measurement floor, it is unlikely to be associated with further or faster disease progression.[42] The implication of disc haemorrhages at such locations remains a contentious issue.

Case: Follow-up 3—treatment titration

At her next follow-up three months later, the superior disc haemorrhage had resolved, and again there was no change in structure or function (Figure 3). However, the IOP had crept up to 12 mmHg in the treated eye. There were no adverse effects to latanoprost and she was reportedly compliant. In combination with the history of recurrent disc haemorrhages and upward creeping IOP, the treatment regimen was increased to latanoprost/timolol combination eye drop (Xalacom) to reduce the IOP to target levels. As per the above, her usual IOP review check was scheduled for six weeks' time.

Are there other options for management in the future?

Upcoming novel management options

Although workflow charts and guidelines are useful for clinical practice (Figure 4), we are moving now towards patient-tailored medicine approaches, and it is likely that more steps and further considerations will be added into the mix.

Since the original NHMRC publication,

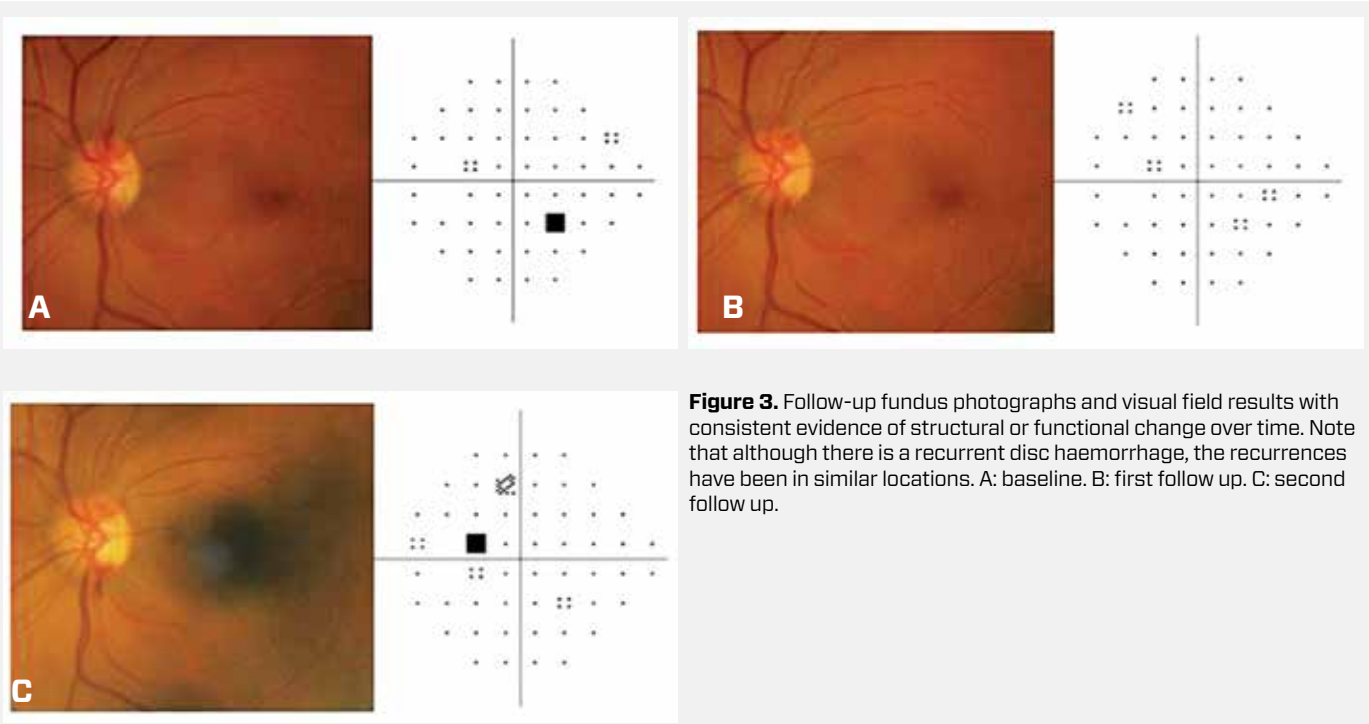

Figure 3. Follow-up fundus photographs and visual field results with consistent evidence of structural or functional change over time. Note that although there is a recurrent disc haemorrhage, the recurrences have been in similar locations. A: baseline. B: first follow up. C: second follow up.

Australian optometrists have gained access to more medication options: preservative-free bimatoprost (Lumigan) and its combination form with timolol (Ganfort), tafluprost (Saflutan) and brimonidine with stabilised oxychloro complex (Alphagan-P). These are worth considering for patients with ocular surface disease, especially those who will likely be on long-term treatment. Practitioners should refer to the Optometry Australia table of anti-glaucoma medications (pages 14-15).

Recent breakthroughs in pharmacology have yielded a number of novel anti-glaucoma medications that are available in foreign markets. Latanoprostene bunod[43] and rho kinase inhibitors[44] have been increasingly used in Japanese and United States markets and will hopefully eventually reach our shores. These medications are unique in providing further IOP reduction by exploiting the trabecular outflow pathway that has been traditionally limited to pilocarpine use.

As a drop-sparing alternative, minimally invasive glaucoma surgery (MIGS) will likely proliferate in Australia, given the new Medicare Benefits Schedule item numbers for ophthalmologists. Studies have demonstrated the efficacy of this technique in reducing IOP and also the burden of drop usage in patients with glaucoma.[45]

Finally, alternative drop delivery platforms have also been considered to address issues with patient compliance. Sustained release implants such as Intracameral implants[46] and silicone rings[47] have undergone clinical trials, with some promising results in IOP reduction for up to three months. In the future, we are likely to see more avenues for patients who are challenged by compliance.

Conclusions

By taking a step back and reappraising the way we manage our patients with glaucoma, we can start to see nuances in patient care. Aside from the topics discussed above, it is important to remember that scientific work is continually being added to the body of literature, and being careful and critical of the evidence is important in providing optimal patient care.

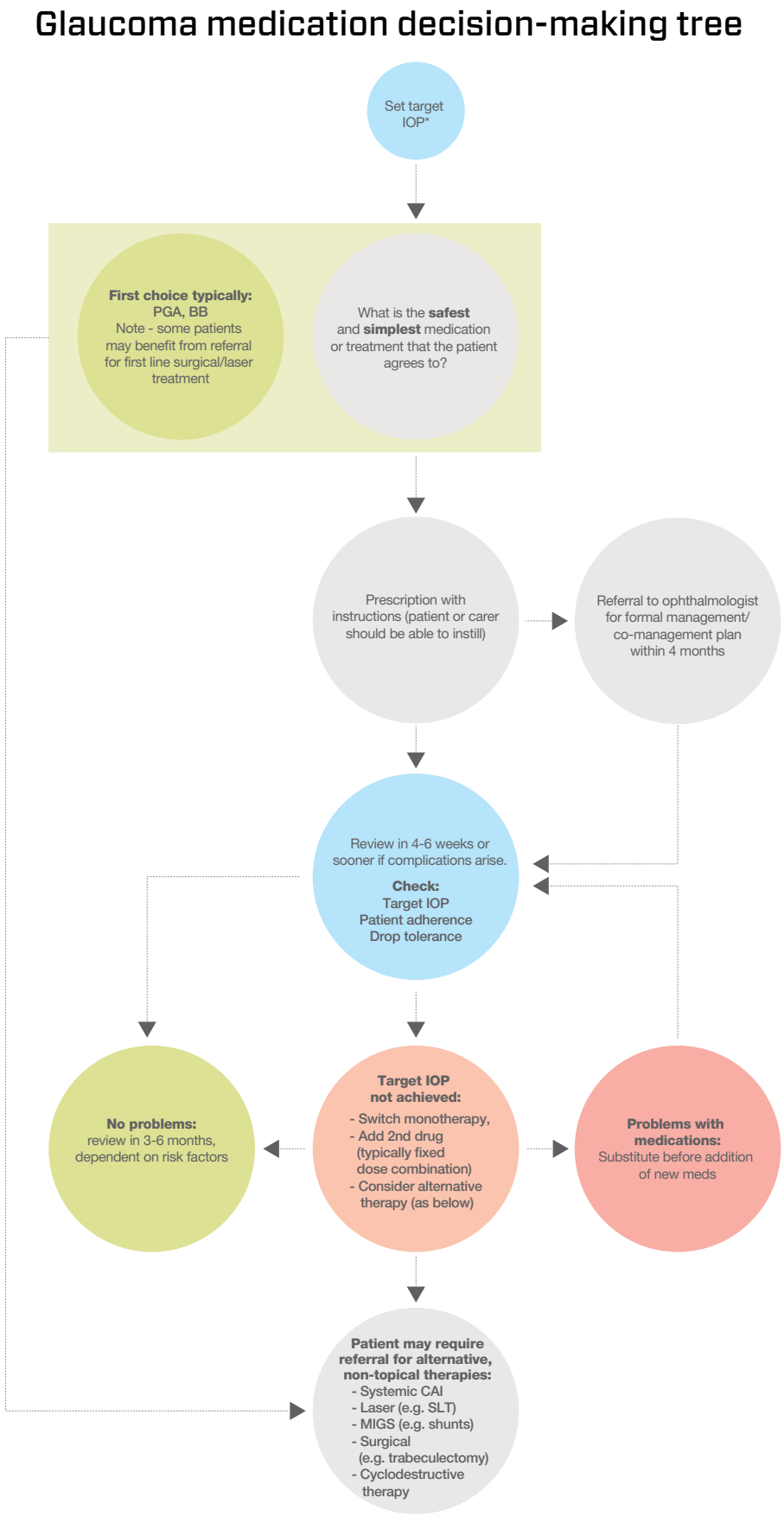

Figure 4. Sample medication decision making tree. (Adapted from the NHMRC glaucoma guidelines 2010.)

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CLINICAL AND EXPERIMENTAL OPTOMETRY

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Relating optical coherence tomography to visual fields in glaucoma

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Glaucoma damages retinal ganglion cells, manifesting in the clinical signs of neuroretinal rim loss, thinning of the retinal nerve fibre layer and visual field sensitivity loss. When patients, either with glaucoma, or at risk of glaucoma, present in clinical practice, the managing clinician will assess structure, by observing the optic nerve and retinal nerve fibre layer with ophthalmoscopic techniques and optical coherence tomography (OCT), and function, by conducting visual field analysis.

Most commonly, this information is assessed by the clinician separately, requiring a judgement on whether there is glaucomatous progression on either one of these measures, and whether there is alignment. The information obtained from this structure-function assessment can, however, be combined using a structure-function map to facilitate the diagnostic and monitoring process.

In their article 'Relating optical coherence tomography to visual fields in glaucoma: structure-function mapping, limitations and future applications,' Drs Jonathan Denniss, Andrew Turpin and Allison McKendrick discuss these structure-function maps and how they aid clinical practice, with particular focus on customised structure-function maps and the advantages these offer.

To accurately assess the relationship between structure and function at specific locations, OCT and visual fields plots need to accurately align. This presents a particular challenge due to the anatomy of the retina – for example, retinal ganglion cells at the macula are displaced from their photoreceptors resulting in a spatial shift between the damage at the retinal ganglion cells (structure) and the location of corresponding visual field loss (function). Solving this conundrum is key to enabling these existing tools to be used more accurately for diagnostic purposes.

OCT measurements are taken from the region surrounding the optic nerve, capturing the thickness of the retinal nerve fibre layer at that point. These measurements are then related to the visual field result based on the trajectory of the retinal nerve fibre layer, such as arcuate field loss that commonly presents in glaucoma. The structure-function maps proposed take this relationship into account.

A new area now being addressed is establishing this relationship in the macular region. The spatial shift between the damaged retinal ganglion cells at the macula and the location of the visual field damage has been explored by obtaining population averages of the length of Henle fibres and hence the structure-function displacement.

Both proposed approaches, at the optic nerve and at the macula, use population averages and hence carry the inherent assumption that these measurements apply to all eyes. This is clearly not the case given the variability in factors such as the pathway of retinal ganglion cells, axial length and optic nerve head position relative to the macula, to name a few. To that end, recent developments in this area have proposed patient-customised structure-function maps based on individual anatomical variations and have shown promising results in both resolution and repeatability.

The main application of such personalised structure-function maps is their combination to establish more accurate diagnosis or progression of glaucoma. New applications include the selection of the targeted region to be tested by visual field analysis based on the OCT data, as well as using the OCT data to modify the visual field testing threshold, for example, by making predictions of the sensitivity at each visual field location based on the OCT results, and then using these predictions as the starting point for the visual field test.

Current research is developing the means to merge the information obtained from OCT and visual field analysis to increase the efficiency and accuracy of diagnosis and monitoring of progression. The customisation of these methods and their use in order to better target visual field testing offer great promise for glaucoma management in the near future.

Denniss J, Turpin A and McKendrick A M Relating optical coherence tomography to visual fields in glaucoma: structure–function mapping, limitations and future applications. *Clin Exp Optom*. 2018 Nov 29. doi:10.1111/cxo.12844. [Epub ahead of print]

Diamox for acute angle closure glaucoma

A New Zealand approach

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Patients with acute primary angle closure may present to their optometrist with a variety of symptoms. This case illustrates an acute presentation which highlights the management of the condition with both topical and oral medications.

CASE REPORT

A 71-year-old Pacific Islander female, Mrs F, was seen in the Emergency Eye Clinic at Greenlane Hospital, Auckland at 3:15pm. She presented with a two-day history of a painful and red right eye with reduced vision. She also mentioned that the eye was aching for approximately four days prior to becoming red. The left eye was asymptomatic. She was bilaterally phakic and her ocular history was positive only for bilateral pterygium excision eight years earlier. She had type 2 diabetes mellitus, diagnosed nearly 20 years earlier with a HbA1c of 63 mmol/mol. She also had hypertension and hypercholesterolaemia which were controlled with metoprolol and atorvastatin.

She had approximately +2.00 D of hypermetropia in each eye, which gave vision of RE 6/18 (no improvement with pinhole) and LE 6/9. IOPs with the Icare tonometer were RE 68 mmHg LE 17 mmHg. Applanation tonometry measured RE 64 mmHg LE 16 mmHg.

On slitlamp examination, she showed diffuse moderate conjunctival injection in the right eye and a white conjunctiva in the left eye. The right eye showed diffuse corneal oedema with microbullae, while the left eye cornea was clear. Van Herrick assessment showed narrow anterior chambers of both eyes.

One drop of Alcaine (proxymetacaine 0.5%) was instilled in each eye and then two drops of glycerol BP 100% were instilled in the RE to better visualise the right anterior chamber during gonioscopy and the posterior of the eye by temporarily dehydrating the corneal epithelium osmotically. Gonioscopy showed a completely closed angle in the right eye with no peripheral anterior synechiae (PAS) (Figure 1). The left anterior chamber was closed superiorly and temporally, open to Schwalbe's line nasally and the inferior angle was open to the posterior trabecular meshwork.

Both crystalline lenses showed moderate nuclear sclerosis. Undilated views of the optic nerve heads showed healthy neuroretinal rims with no disc swelling.

A diagnosis of right eye acute primary angle closure was made. The patient had no known drug allergies but as she was diabetic, her last renal function results were checked. Her glomerular filtration rate (eGFR) was 86 mL/min/1.73m2 and her creatinine level was 63 umol/L. As her kidney function was excellent, she was given a stat dose of 500 mg Diamox (acetazolamide) orally as well as topical Iopidine (apraclonidine 0.5%), Pred forte (prednisolone acetate 1%), timolol 0.25% and Trusopt (dorzolamide 2%) to the right eye.

By 4:40pm, her pressure had reduced to right eye 30 mmHg. Pilocarpine 2% was instilled in each eye and she underwent bilateral YAG laser peripheral iridotomies (LPIs) at 5.30pm. Good pigment gush was noted in each eye during the procedure (Figure 2) from a 1 mm superior patent PI (Figure 3). At 6:30pm, her right eye pressure was 17 mmHg. She was therefore discharged home on Pred forte six times per day, Combigan (brimonidine 0.2%/timolol 0.5%) and Azopt (brinzolamide 1%) twice daily, all to the right eye as well as to continue the oral Diamox 250 mg twice daily with review set to the next morning to recheck the IOP and tolerance of the oral Diamox.

The next morning, her aided vision was RE 6/18 (pinhole 6/15) and LE 6/7.5. IOPs were RE 9 mmHg LE 11 mmHg and she had tolerated the Diamox well. The LPIs were open and patent, and gonioscopy showed that the left eye was open, but the right eye superior and temporal angles were still closed, the nasal angle was open to Schwalbe's line and the inferior angle had opened to posterior trabecular meshwork. She was instructed to continue her topical medications and her Diamox was discontinued. Review was again set at one day.

The next day her vision had further improved to RE 6/15 (pinhole 6/12) and LE 6/9+. IOPs were RE 15 mmHg LE 10 mmHg. As her angles were still narrow despite the LPIs, she continued her topical medications until she underwent successful cataract extraction three weeks later in her right eye and two months later in her left eye.

At the final follow-up post bilateral lens extraction, her vision was 6/7.5 unaided in each eye. Gonioscopy showed deep and quiescent anterior chambers with no PAS. Her optic nerve heads showed 0.3 cupping in each eye with normal retinal nerve fibre layer thicknesses in each eye on the OCT scans. She was therefore discharged back to her optometrist for

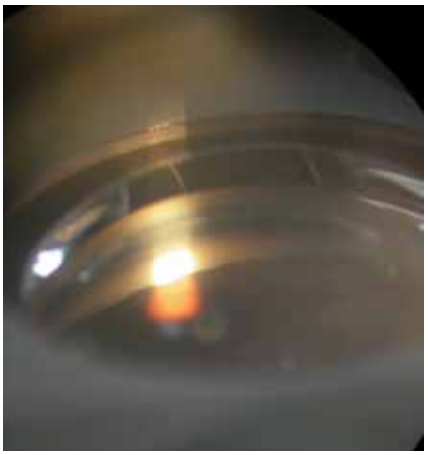

Figure 1. A completely closed angle in the right eye revealed by gonioscopy

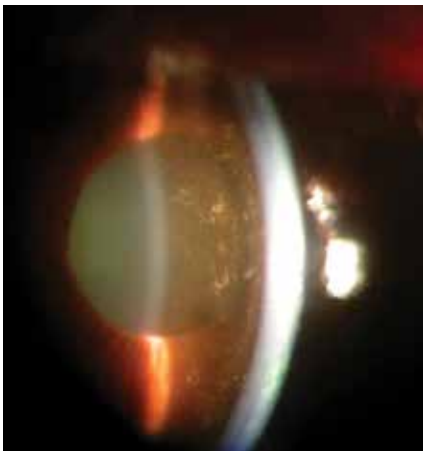

Figure 2. Pigment release into the anterior chamber immediately following the laser peripheral iridotomy

Figure 3. Retro-illumination shows a patent LPI in the superior position

annual diabetic retinopathy checks.

Discussion

Diamox (acetazolamide) is a carbonic anhydrase inhibitor (CAI) which acts as a diuretic, eliminating fluid from the body.[1] This property makes it useful for a number of conditions, including the treatment of acute primary angle closure, idiopathic intracranial hypertension, altitude sickness and heart failure.[2]

Carbonic anhydrase is an enzyme found in many tissues in the body, including red blood cells, the ciliary body and the proximal tubule of the kidneys. Since carbonic anhydrase actively allows the re-absorption of bicarbonate, sodium and chloride, inhibition of it causes excretion of these ions together with excess water thus lowering blood pressure, intracranial pressure and intraocular pressure.

The excreted bicarbonate ions lead to a reduced blood pH which causes a compensatory hyperventilation with deep respiration, known as Kussmaul respiration.[3] This results in increasing levels of blood oxygen along with decreasing levels of blood carbon dioxide. In the eye this results in a reduction in aqueous humour. As was demonstrated in the case of Mrs F, the use of acetazolamide may control IOP until the underlying cause of the raised IOP can be addressed. This may include LPIs, a clear lens extraction (CLE) or a cataract extraction with intra-ocular lens insertion. Rarely, it may also be used in primary or secondary open angle glaucoma, such as angle recession or rubeosis, where topical medications are insufficient or not well enough tolerated to control IOP until a surgical procedure such as a trabeculectomy, bypass tube or stent can be performed.

Contraindications to the use of CAIs include known hypersensitivity to acetazolamide or other sulphonamides or those with sulphur allergies. Additionally, bodily states with adjusted blood chemistry also contraindicate the use of CAIs, such as hyperchloremic (excess blood plasma chloride level) acidosis, hypokalemia (low blood potassium) and hyponatremia (low blood sodium). Similarly, patients with reduced renal function (such as patients with end-stage diabetic renal failure) must have any potential benefits from the use of the drug balanced against the risk of further worsening renal function and altered blood chemistry. This is often best done by speaking directly with the patient's renal physician who will usually recommend a titrated dose of 125 mg four times a day.

Side effects with CAI use are common and include paraesthesia (tingling sensation of the extremities, especially the fingers), fatigue, drowsiness, depression, experiencing a bitter or metallic taste, nausea and/or vomiting, abdominal cramps and diarrhoea. Vomiting associated with acetazolamide may be severe enough to require it to be administered intravenously. Side effects are usually proportional to dosages and may be reduced by lowering the frequency and/or concentration of dosages. Varying levels of sensitivity to the drug may be experienced by patients, ranging from mild to anaphylaxis and also the potentially life-threatening Stevens-Johnson syndrome.[4]

Oral and intravenous acetazolamide have been found to be potentially teratogenic at high levels in mice studies and are therefore classified as pregnancy category B3 drugs in Australia. Despite the lack of hard evidence of acetazolamide causing birth defects in humans, the drug should be avoided if possible during pregnancy and breastfeeding.

Use in NZ, use in AUS

In New Zealand (NZ), oral Diamox may be used by therapeutic optometrists in the treatment of acute primary angle closure. Currently, Australian optometrists may recommend the drug to be prescribed via a GP. A stat dosage of 500 mg is recommended for adults over 50 kg and 250 mg for adults under this weight.[2] Prescribing optometrists in NZ are advised to liaise with the patient's GP to discuss whether the drug is suitable for the patient, and also with an ophthalmologist to arrange definitive treatment of the acute angle closure.

Since July 2014, optometrists in NZ have been able to prescribe oral medications for ophthalmic

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Diamox

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conditions. This can include non-emergency presentations of glaucoma but is usually limited to those working in specialty glaucoma clinics in hospitals in conjunction with glaucoma-specialist ophthalmologists.

Acute primary angle closure has traditionally been managed by performing LPIs once the IOP has been reduced and any associated corneal oedema has cleared. CLE was later performed if the anterior chamber failed to open sufficiently in response to the LPI. However, in 2016, the landmark EAGLE study showed that CLE has become the definitive treatment of acute angle closure glaucoma.[5]

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Clinical management of

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Herpes simplex keratitis (HSK) is a common diagnosis in primary care but its diagnosis can be delayed or be easily missed. HSK can cause permanent visual loss due to corneal scarring and therefore it is important to diagnose early.

The incidence of herpes simplex virus type 1 (HSV-1) is reported to be 76 per cent while that of herpes simplex virus type 2 (HSV-2) is 12 per cent in Australia.[1] Traditionally it was assumed that HSV-1 was oro-facial and HSV-2 was genital, however changing attitudes mean that is no longer the case with cross infection now showing up with increasing frequency.

CASE REPORT

A 25-year-old female presented to the emergency department with a one-week history of red left eye and constant watering. Her general practitioner had prescribed chloramphenicol for presumed conjunctivitis.

On examination, visual acuity was 6/6 and the pupils were reactive to light and accommodation. Slitlamp examination revealed significant injection of the conjunctiva (Figure 1). Corneal sensation was decreased and fluorescein examination revealed a dendritiform or arborising lesion near the limbus (Figure 2).

On closer questioning, the patient revealed she had had previous cold sores on her lips on a few occasions.

The differential diagnoses:

- Herpes simplex keratitis (HSK)
- Healing corneal abrasion
- Recurrent corneal erosion
- Acanthamoeba keratitis
- Varicella zoster virus (VZV)

On the basis of classical appearance, HSK is the most likely diagnosis and aciclovir 3% ointment was commenced five times daily. The patient was reviewed after one week when almost complete resolution was noted with a faint sub-epithelial scar. At this point as the lesion was off the visual axis a decision was made to continue aciclovir 3% ointment for an additional week. At the third and final visit, no epithelial staining was visible and the patient was discharged.

Around six months later, the patient returned complaining of photophobia and reduced visual acuity. Visual acuity fell to 6/9 and slitlamp examination revealed an area of corneal oedema with keratitic precipitates on the endothelial side of the lesion and occasional cells in the anterior chamber. Corneal sensation was again reduced and intraocular pressure (IOP) was normal.

The differential diagnoses at this point were:

1. Herpes simplex endothelial keratitis (disciform keratitis)
2. VZV disciform keratitis
3. Interstitial keratitis – including HSV but consider other pathogens such as fungi and acanthamoeba

Disciform keratitis or HSV endothelial keratitis was diagnosed and topical dexamethasone 0.1% four times daily was commenced along with oral valaciclovir 500 mg twice

herpes simplex keratitis

Diagnosis, risk factors and treatment

daily. Within four weeks, there was resolution of the symptoms and signs. Steroid drops were tailed off but on the basis of recurrence of HSK, oral valaciclovir 500 mg once daily was continued as prophylaxis for one year.

Diagnostic tests

In most cases, the diagnosis is fairly clear from the history and clinical examination especially when there is associated reduced or even absent corneal sensation. However, in certain situations further investigations can be of value particularly in the setting of contact lens wear. The most important and difficult differential diagnosis to exclude is that of acanthamoeba keratitis.

Confocal microscopy can be useful to diagnose acanthamoeba, though the availability of this device is low and it is a tertiary level investigation.

Culture is the gold standard for diagnosis of HSV but while specificity is high, sensitivity is low and it requires the availability of a skilled laboratory. Results can take time to become available.

Polymerase chain reaction (PCR) is now the most common method of diagnosis in most hospital eye services and provides the highest level of sensitivity (98 per cent) and specificity (100 per cent).[2] However, it cannot differentiate from active viral shedding and asymptomatic viral shedding which is normal.

Given the high incidence of HSV-1 infection in Australia, serology by way of a blood test is of limited use as it can only indicate infection at some point in the past.

Risk factors

• **Corticosteroids** – often prescribed for a number of ocular diseases as well as following surgery. They are strongly implicated in the reactivation of HSK.

• **Prostaglandin analogues** – commonly prescribed for glaucoma and to mediate inflammation (the effects are clear in many patients with red eyes), but have also been reported to reactivate HSK.[3]

• **Surgery** – HSK reactivation has been reported after many ocular surgical procedures including cataract surgery however it is unclear if topical steroid use following surgery was the cause.

• **Ultraviolet light** – reported to be a factor in the reactivation of labial HSV-1 however the evidence for corneal HSV-1 is imprecise.[4]

Clinical presentation

Herpes simplex keratitis can present in three main forms with the most common being epithelial disease. Other forms are endothelial and stromal keratitis which are both often labelled as disciform keratitis. It is important to classify HSK appropriately as it crucially affects the management. It must also be understood that HSV and VZV can both cause a multitude of ocular diseases and are not limited to the cornea.

HSV stromal keratitis typically follows previous HSV epithelial keratitis though it can be the initial presentation of herpetic disease. It

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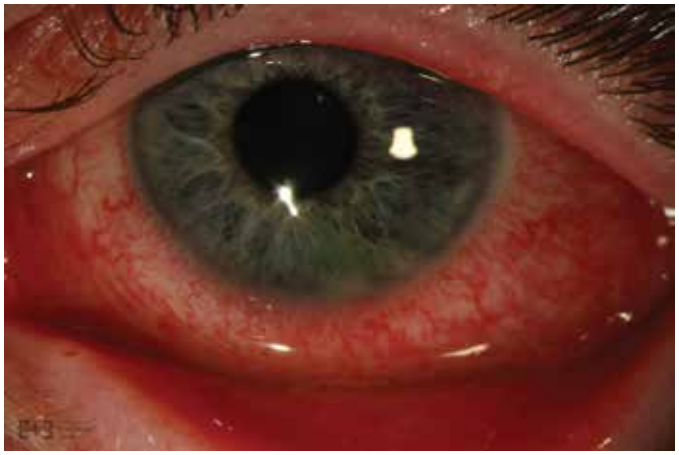

Figure 1. Initial presentation. Slitlamp examination revealed significant injection of the conjunctiva.

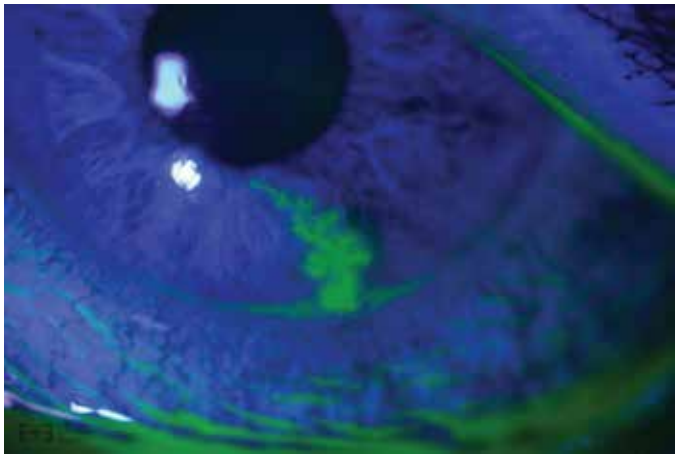

Figure 2. Fluorescein staining reveals a dendritiform or arborising lesion near the limbus

Herpes simplex keratitis

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is caused by an immune response to retained viral antigens in the stroma. Rarely a necrotising interstitial keratitis that is believed to be due to live viral proliferation in the stroma can develop leading to corneal perforation. Stromal keratitis with ulceration should be assumed to be necrotising interstitial keratitis.

Unlike epithelial disease which can resolve on its own even in the absence of therapeutic intervention, stromal disease is not self-limiting and therapeutic intervention must be initiated. Failure to do so can lead to catastrophic consequences.

HSV endothelial keratitis can present both as a disciform type as well as with diffuse corneal oedema. It should be suspected in any unilateral case of acute corneal oedema and often presents with keratic precipitates on the endothelial surface in addition to overlying corneal oedema.

Treatment

The first line treatment for epithelial herpes simplex keratitis is topical aciclovir 3% ointment. The only TGA (Therapeutic Goods Administration) and PBS (Pharmaceutical Benefits Scheme) subsidised treatment available for HSK in Australia has been Zovirax, however GlaxoSmithKline (GSK) has announced the cessation of this product and final shipments in Australia ran out in December 2018. The TGA have provided a temporary exemption for AciVision (aciclovir) 30mg/g eye ointment expiring 31 August 2019 for now.[5] It is important to note that it is not a TGA-registered product and, as such, it is also not subsidised on the Pharmaceutical Benefits Scheme (PBS).

In New Zealand aciclovir 3% is available as ViruPOS (aciclovir 3%) and is fully subsidised by Pharmac.[6]

Aciclovir resistance[7] is now a real issue and where it is suspected or aciclovir 3% ointment is contraindicated, ganciclovir 0.15% (Virgan) gel three times daily can be considered. It however requires a Special Access Scheme (SAS) Category B approval in Australia. In New Zealand Virgan is available as a section 29 unapproved medicine.

Oral treatment is also an option and the recommended product is valaciclovir 500 mg twice daily or three times daily, though aciclovir 800 mg five times daily is also an option. These products are not listed on the PBS for HSK. When considering oral treatment for epithelial HSK, The Royal Australia and New Zealand College of Ophthalmologists (RANZCO) have recommend via email communication to the membership that it is combined with epithelial debridement and chloramphenicol ointment.

In the setting of HSV endothelial keratitis or stromal keratitis the primary treatment is a topical steroid such as dexamethasone 0.1% or prednisolone acetate 1% in combination with an oral or topical antiviral.[8] There is a suggestion that oral treatment is superior in terms of faster resolution and improvement of visual acuity.[8]

Oral prophylaxis

The role of oral aciclovir 400 mg twice daily to prevent recurrences has been well researched and proven to reduce recurrences of epithelial and stromal keratitis.[9] Valaciclovir has been demonstrated to be as effective with the advantage that it only needs to be taken once daily.[10]

Surgery

In rare circumstances, acute surgical intervention may be required in the setting impending or actual corneal perforation. Corneal transplantation may be required in the setting of chronic corneal scarring on the visual axis.

Conclusion

The morbidity of herpes simplex keratitis should not be underestimated and appropriate therapy depending on anatomic location should be initiated promptly to prevent loss of visual acuity. Oral prophylaxis should be considered in recurrent cases.

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Erratum

In the December issue of *Pharma*, there was an error on the PBS list of medicines.

There are two entries in the product list for 'Alphagan, Enidin.' The second entry is incorrect and the product name should be noted as: 'Simbrinza' not 'Alphagan, Enidin.'

We'd like to thank the eagle-eyed readers who have contacted us to correct the error.

Why are older eyes at greater risk of glaucoma?

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Ageing is a major risk factor for many neurodegenerative diseases.[1-4] Glaucoma is one such condition, where the incidence and prevalence increases almost exponentially with age.[4]

It is not simply an elevation in intraocular pressure (IOP) that causes this age-related increase, as IOP does not consistently increase with age.[5] In Japan, there is a trend for IOP to decrease with age.[6] This seems paradoxical as the incidence and prevalence of glaucoma in Japan is comparable to Western countries.[7] How advancing age increases the risk of glaucoma remains poorly understood.

Age-related changes to the eye are well documented, with the number of retinal ganglion cells gradually decreasing with age.[8] However, age-related changes might occur at different rates in different eyes. Our eyes are constantly exposed to a range of stressors such as oxygen-free radicals and fluctuations in eye pressure. Low intensity stressors drive processes that maintain and repair cells. Indeed, our eyes encounter regular intermittent increases in pressure that arise from a range of behavioural and physiological variables that include blinking, eye movements, eye rubbing, changes in posture and thoracic pressure. An increase in the intensity of stressors can overwhelm the capacity of the ageing system to repair itself, thus leading to disease.

We know from experimental models that when exposed to an acute reduction of blood supply[9] or increased mechanical stretching,[10] eyes of older rodents demonstrate greater ganglion cell loss compared with younger ones. Similarly, older eyes show a poorer ability for retinal ganglion cells to recover from IOP elevation.[11] Poorer recovery is indicative of a reduction in the capacity for repair in older eyes. Not surprisingly, experimental intervention to reduce oxidative stress and improve the capacity for retinal neurons to generate energy (in mitochondria) improved ganglion cell recovery from stress in older eye.[11] These data speak to the idea that older neurons already have an impaired capacity to handle oxidative stress[12] and are therefore less able to repair following additional IOP-related stress. The failure of repair mechanisms will eventually lead to cell death and vision loss.

Age-related changes are not limited to ganglion cells; these effects can be seen in all structures in the eye and optic nerve. These tissues include blood vessels and associated glia that are critical for supporting the ganglion cells, as well as the cells that are responsible for the maintenance of aqueous outflow pathways and connective tissue at the lamina cribrosa. Age-related changes to connective tissue can have a significant impact on the intensity of stress.

It is known that in older eyes the lamina cribrosa[13,14] and peripapillary sclera become stiffer.[15,16] This stiffness appears to occur as there is excessive collagen, less elastic fibres (elastin) and more cross-linking in the three-dimensional network of support tissue around cells in the peripapillary sclera and lamina cribrosa.[17]

These age-related changes lead to connective tissue that is less compliant and therefore less able to absorb force, such as those associated with fluctuations in IOP. Studies using *ex vivo* approaches have shown that eyes with a stiffer outer coat manifest larger increases in IOP (that is: bigger pressure spikes) for a given increase in volume.[18,19] While one would presume that eyes better able to absorb IOP elevation would show less neural dysfunction, we sought to formally test this idea in our experimental model.

In our recent study[20] using a rodent model, we measured the change in ganglion cell function (light-induced electroretinogram responses), ocular blood flow (doppler optical coherence tomography) and retinal structures (optical coherence tomography) to increased pressure difference between the inside and outside of the eye (also known as the optic nerve pressure difference, or in humans the trans-laminar pressure gradient) in young and older eyes. A higher-pressure difference was induced by either elevating IOP or reducing intracranial pressure.

By comparing rodent ages that model human eyes in their twenties and those that are in their fifty to sixties, we show that older rat eyes were stiffer (Figure 1B) and showed less stretching when the optic nerve pressure difference was increased compared with younger eyes (Figure 1A). Our data also suggest that as the older and stiffer eyes absorbed

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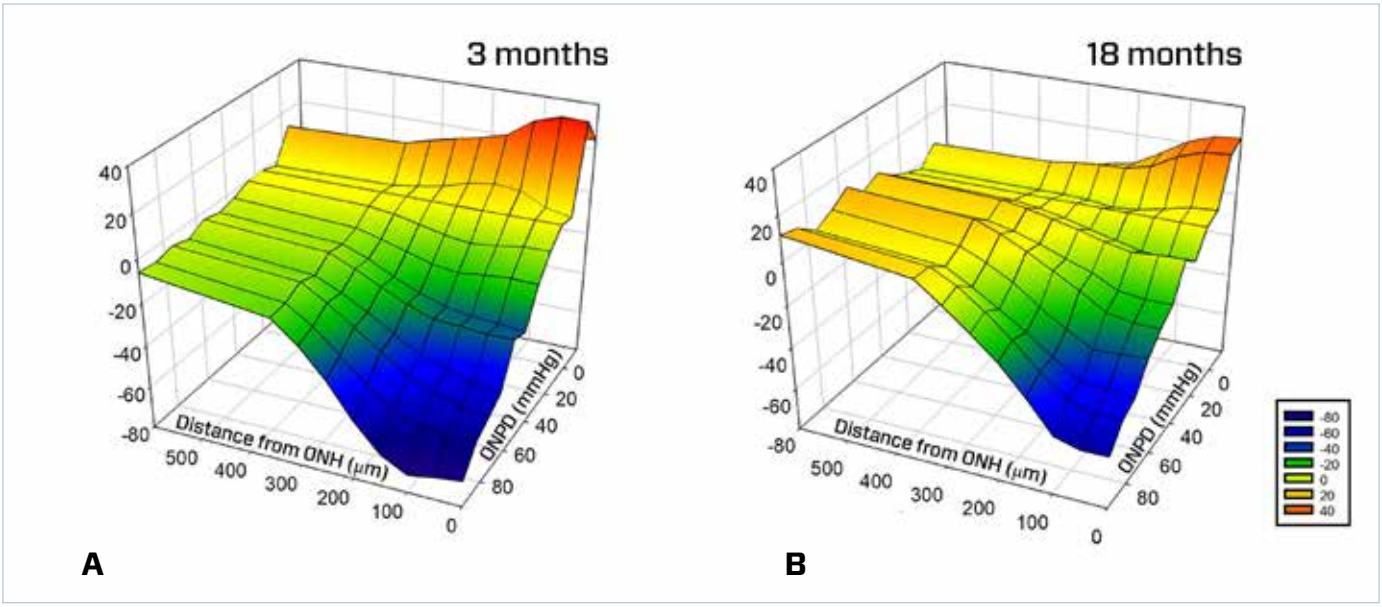

Figure 1. Anterior surface deformation (µm). Graphs show that as optic nerve pressure gradient increased, the surface of the eye in and around the optic nerve was pushed backward. A: Younger eyes actually showed more backward bowing than B: older eyes. This would indicate that older eyes are less able to absorb IOP elevation.

Older eyes

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less of the stress and strain associated with IOP elevation, this resulted in more retinal nerve fibre layer compression. This we believe accounts for a greater reduction in ganglion cell function with IOP elevation in older eyes.

Our data supports the idea that age-related changes biomechanically increases the intensity of stress encountered by ganglion cells. Higher intensity or larger doses of stress are more likely to overwhelm cellular protective and repair mechanisms, perhaps accelerating changes that result in disease. Although how ageing increases the risk of glaucoma and other neurodegenerative disease is complex, investigations in this area are likely to yield significant insights into glaucoma pathogenesis.

In the clinical domain, researchers have been keenly interested in developing tests for eyes that have increased biomechanical stress, and thus are at greater risk of glaucoma. One way to do this is to place a fixed amount of pressure on the eye and test the capacity of it to absorb this pressure. This is essentially the principle underlying corneal hysteresis measurement.[21] Ophthalmodynamometry has also been used to induce mild IOP elevation and using optical coherence tomography researchers have attempted to quantify the deformation in the optic nerve and peripapillary sclera.[22] Perhaps, in the future we might better identify those at risk of glaucoma by stress testing the eye, such is the case with the exercise treadmill test to expose those hearts that cope poorly with exertion.

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