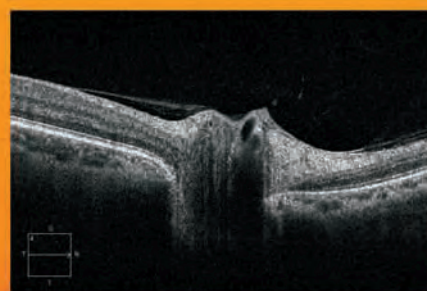
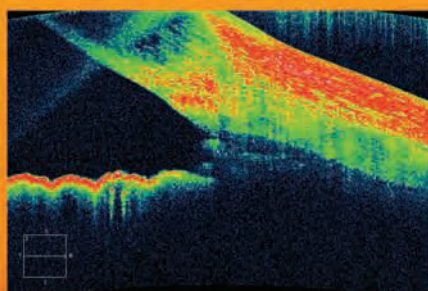
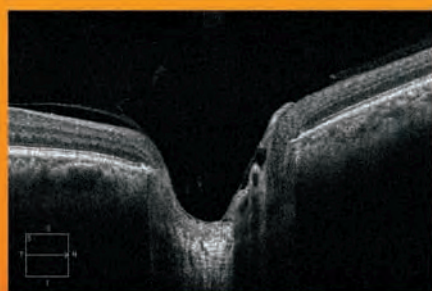


THE Glaucoma Handbook



OPTOMETRIC GLAUCOMA SOCIETY

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1 | Introduction

I would like to welcome you to the fifth edition of the Glaucoma Handbook, a publication developed under the auspices of the Optometric Glaucoma Society (OGS). This handbook is meant to serve as a guide to the diagnosis and management of glaucoma and is not an exhaustive review. The material includes a review of basics in regards to glaucoma diagnosis and therapy while providing new insights into the condition. Our goal with each new edition is to keep the material fresh and up-to-date. In certain sections, there is new information while all chapters have been updated. Glaucoma diagnosis and management is in an evolutionary phase with small improvements occurring. In regards diagnosis, spectral domain OCTs have been available for 18 months with several companies now building these devices. When first launched, OCT analysis schemes used older methods to assess the data such as TSNIT curves and optic disc cross-sectional cuts. The 3-D cube of data was not utilized except visually but this is now changing with new schemes being developed to evaluate this huge amount of data. On the cover are images taken with the Carl Zeiss Meditec, inc. Cirrus Spectral OCT that provide examples of where imaging is going. Imaging of both the anterior and posterior segment are available, with resolution not previously possible in commercial instruments. In these examples, the angle and optic disc from a healthy individual are seen along with an image of optic disc drusen. The spectral OCTs are evolving as both the Cirrus and RTVue can also image the anterior segment, and software for glaucoma progression is available on several instruments.

We should see the release of the Heidelberg Edge

Perimeter (HEP) shortly which continues in the quest for early perimetric detection of glaucomatous damage. Whether the HEP perimeter is a step forward will not be known for several years. Another new functional test under development is pupil perimetry, which is an objective method to assess central vision and reduces patient involvement. Similar to the HEP, it will take several years before we know if this will be a viable test. In regards to therapeutics, we are anxiously waiting for the next class of drugs. It has been several years since a new glaucoma drug was made available with combination drugs being the most recent addition to glaucoma medical therapy. Glaucoma surgery is evolving, however slowly, with the quest for procedures that reduce IOP with fewer complications.

I would like to thank the members of the OGS for their support and help in developing these materials. I would like to recommend the OGS electronic journal, which is available free of charge. It comes out quarterly and covers many different aspects of glaucoma. One may sign up for this at www.optometricglaucomasociety.org. On behalf of the OGS, I would like to thank our team of authors who contributed to this effort. I would also like to thank Karen Fixler, Ravi Pherwani, Tom Wright and Jill Burdge from Pfizer for their continuing support of the OGS, and specifically for the unrestricted grant that allowed us to continue with this publication. We hope that you find this handbook useful.

Murray Fingeret, OD

Executive Vice-President, Optometric Glaucoma Society
Editor, The Glaucoma Handbook

2 | The Diagnosis of Glaucoma

John G. Flanagan, PhD, MCOptom

Most glaucomas are asymptomatic until the late stages of the disease, and therefore a careful, comprehensive eye examination, including history, is essential to the early diagnosis. The majority of information important in the patient's history relates to our knowledge of the disease's epidemiology and risk factor analyses. Age and race have clear clinical implications for the risk of developing glaucoma, with peoples of African descent showing a four to five times greater prevalence, a higher risk of blindness and a tendency to be diagnosed at a younger age. More recently it has been shown that while younger Hispanic-Americans develop primary open-angle glaucoma (POAG) at a rate similar to Caucasian-Americans, the ratio increases dramatically in older age, eventually exceeding even African-American rates after the age of 75. Pigmentary glaucoma is more common in Caucasians, as is exfoliative glaucoma—the latter appearing to cluster in certain regions; for example, the Scandinavian countries. Age and ethnicity are also important in regards to the angle closure glaucomas, which will be discussed in Chapter 12. Risk factors for the development of this condition include older age as well as individuals of Asian heritage.

Family history is well established as a risk factor for glaucoma. Having a sibling with glaucoma increases a person's chance of developing POAG 3.7-fold, according to some evidence. The prevalence of POAG in people having a first-degree relative with POAG is estimated to be between 4% and 16%. Up to 25% of patients with glaucoma are reported to have a positive family history. The overall proportion of POAG attributable to genetics is thought to be around 16%.

Ocular history is very important, as well. An essential aspect of any initial glaucoma diagnosis is a careful review of previous ocular findings. Ocular hypertension is strongly associated with an increased risk of POAG, as are specific aspects of the optic nerve and nerve fiber layer appearance. Indeed, risk assessment tools have been developed following the Ocular Hypertension Treatment Study (OHTS) and the European Glaucoma Prevention Trial (EGPS) and their application is discussed in Chapter 5. There has been a renewed interest in the risk related to ocular perfusion pressure (OPP), the difference between blood pressure (particularly diastolic) and IOP. Low OPP at the optic nerve may lead to ischemic insult and ultimately initiate glaucomatous optic neuropathy. The Barbados Eye Studies confirmed their earlier finding that there was an approximately three-times increased risk of developing OAG in those with low OPP at baseline. They also found an increased risk of progression. This has also been reported by the Early Manifest Glaucoma Trial (EMGT) in an 11 year follow up that reported patients with low OPP to be at 1.5-times increased risk of progressive disease. Of less diagnostic importance, but still worth documenting, are myopia and a history of systemic disease such as diabetes mellitus, systemic hypertension, vasospastic disease, autoimmune disease and severe hypotension.

TONOMETRY

Intraocular pressure (IOP) remains the single most important risk factor for the development of glaucomatous optic neuropathy, and its measurement is vital in the initial diagnosis and management of the glaucomas. It is also the only major risk factor that can be treated. There has been much recent interest in the ability to moni-

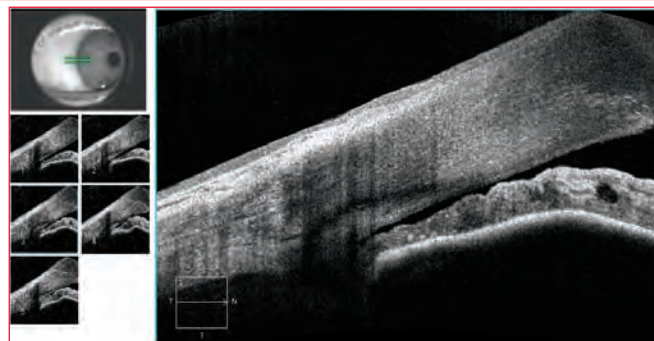


Figure 1. Anterior segment imaging using the Cirrus HD-OCT, showing multiple scans of a narrow angle. (Images courtesy of Carl Zeiss Meditec, Inc.)

tor continuous, 24 hour IOP, in order to evaluate sleep IOP profiles and potentially to combine such data with measures of diurnal blood pressure. Such technology is not yet available but promises to be a significant advance of great clinical potential. See Chapter 3 for a discussion of IOP, its clinical importance and relationship to corneal thickness and corneal biomechanics.

GONIOSCOPY

The careful examination of the anterior chamber angle is essential in evaluating glaucoma suspects and diagnosing glaucoma. Gonioscopy enables the visualization of the anterior angle and its assessment permits the exclusion of angle closure, angle recession, plateau iris or secondary angle block as the cause of raised IOP. Gonioscopy is most commonly performed indirectly by using a contact lens with a mirror system that overcomes the inherent total internal reflection of the angle anatomy. The angle is graded to relate information of its visible anatomical features (see gonioscopy.org for review, including excellent video clips). Several non-contact OCT devices can be used to evaluate the angle; these include the stand alone Visante (Carl Zeiss Meditec) and Slit Lamp (SL)-OCT (Heidelberg Engineering), and the analysis modules available on some of the new generation spectral domain (SD) OCTs including the RTVue (Optovue Inc.), Cirrus HD-OCT (Carl Zeiss Meditec) and Spectralis (Heidelberg Engineering) (Figure 1). Although considerably more expensive than a classic contact gonioscopy, they have the advantage of being objective and quantitative. In addition, these devices can accurately measure and map corneal thickness. They can also image bleb quality following trabeculectomy and the integrity of peripheral iridotomies. However, due to the nature of OCT its is often not possible to see the complete angle due to the signal being blocked and therefore assumptions need to be made for the positioning of the sclera spur when measuring the angle.

STRUCTURE

Evaluation of the optic nerve head and nerve fiber layer (NFL) is important in identifying early structural damage. Such structural changes frequently occur prior to the presence of repeatable visual function deficits. Clinical evaluation should be performed at the slit lamp using a magnified, stereoscopic view through a dilated pupil. The lens should be handheld. Perform careful, systematic documentation of the neuroretinal rim, including evaluation based on the ISNT mnemonic device. That is, healthy rim tissue should always be thicker in the inferior (I) region, followed in decreasing thickness by the superior (S), nasal (N) and temporal (T) regions. It has been suggested that this clinical schema performs better if the nasal

quadrant is ignored owing to the obscuration of the nasal rim tissue by the nerve head vasculature, resulting in the IST device (this is particularly true when considering the quantitative data provided by imaging devices such as the HRT). Other observations that require documentation include: focal thinning of the rim tissue, vertical elongation of the cup, concentric enlargement of the cup, increased cup depth, saucerization, disc asymmetry, beta-zone parapapillary atrophy and vascular signs such as disc hemorrhage, focal narrowing, beading of circumlinear vessels, bayoneting and nasalization of the vascular tree. The size of the optic disc needs to be evaluated because the cup size correlates directly with the optic disc size. In a healthy individual, the larger the optic disc, the larger the optic cup. The disc size may be qualitatively measured with the small spot of a direct ophthalmoscope, with a fundus lens at the slit lamp or with an optic nerve imaging instrument. Practitioners should use a red-free filter to evaluate the nerve fiber layer (NFL) within two disc diameters of the optic nerve. However it should be noted that modern digital fundus cameras give unprecedented images of the nerve fiber layer and are highly recommended. Several grading systems have been suggested, with the aim of evaluating the level of diffuse NFL atrophy and the identification of localized wedge or slit defects.

FUNCTION

Visual function is generally evaluated by measuring the visual field via standard automated perimetry. In glaucoma, the central vision is not affected until late in the disease process. Consequently there is little diagnostic value in evaluating only central visual function by way of visual acuity. Clinical evaluation of automated perimetry charts remains a standard for the detection of glaucoma. Typical glaucomatous visual field defects were first described by von Graefe in 1869 and result from apoptotic death of the retinal ganglion cells. The field defects reflect damage to the NFL bundles as they track from the optic nerve, although the primary site of damage is thought to be at the level of the lamina cribrosa within the optic nerve. Classic defects include early isolated paracentral, arcuate, nasal step and occasional temporal wedge defects. It is likely that a generalized defect due to diffuse loss of axons is present in many glaucomatous visual fields, but such defects have limited diagnostic value as they are difficult to distinguish from the effects of media opacity and pupil size.

The standard clinical application of static threshold automated perimetry entails the assessment of the central 30 degrees. A variety of threshold estimation algorithms are available, with the faster strategies based on Bayesian methods—for example the SITA strategy found on the Humphrey Field Analyzer (HFA). It is important to re-test abnormal looking visual fields to ensure repeatability, particularly in the naïve patient, as there is a clearly defined learning curve that can mimic early defects. Interpretation can be aided by statistical packages that analyze the data relative to age-matched normal values (Total Deviation), and scan for focal defects by removing the influence of diffuse loss (Pattern Deviation). There are also analyses that judge subjects' intra-test reliability and the symmetry between the upper and lower field, such as the glaucoma hemifield test. It is essential to establish good quality baseline data for both the early diagnosis and the management of manifest disease. Indeed, recent recommendations have stated the need for six fields in the first two years in order to appropriately manage patients with glaucoma. To successfully identify those patients

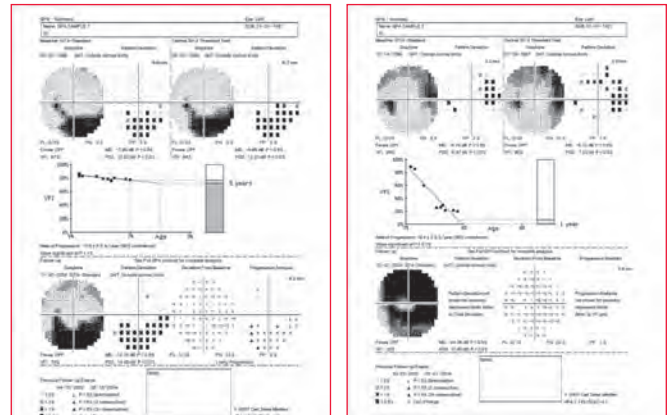


Figure 2. New glaucoma progression analysis printout for the HFA, incorporating the Visual Field Index, which quantifies the rate of progression and illustrates the projected loss. The left printout shows a relatively stable patient with a slow rate of progression, whereas the right printout shows a rapid rate of progression in a patient who underwent a change in therapy before the rate of progression reduced as seen in the last 6 fields plotted in the VFI.

with a $-2\text{dB}/\text{year}$ change, leading to profound loss within seven to eight years, it is necessary to have multiple fields to confidently interpret the measurement within the noise. This was inspired by the important findings of studies such as the EMGT, within which a small but significant percentage of patients exhibited dramatic and rapid progression even at the earliest manifestation of their glaucoma. This is also the thinking behind the excellent new Visual Field Index available for interpretation of rate of progression on the Humphrey Field Analyzer (HFA) (figure 2). There are several standard analyses for glaucomatous progression, the most common being the Humphrey Field Analyzer's Glaucoma Progression Analysis (GPA). The analysis empirically compares serial fields to results collected in a group of patients with stable glaucoma. The original application used age-matched normal data to perform the analysis (Total Deviation), but the EMGT found results to be more accurate when based on the Pattern Deviation analysis, by reducing the influence of diffuse loss.

The relationship between Structure and Function has gained much recent attention and is clearly not as simple as many would hope. However, it is inevitable that we will soon be considering the complexities of this relationship when attempting to diagnose and manage our patients with glaucoma. Indeed the first available combined analysis of Structure and Function will soon be available from Heidelberg Instruments and combines results from the Heidelberg Retina Tomograph (HRT3) and the Heidelberg Edge Perimeter (HEP) (see chapter 4).

The diagnosis of glaucoma requires the clinician to perform a series of tests, including a risk factor analysis, measurement of IOP, assessment of corneal thickness and evaluation of the anterior chamber angle, optic nerve, retinal nerve fiber layer and visual field. The skilled clinician will integrate these results in an attempt to diagnose glaucoma at its earliest manifestation. There is an increasing awareness of the importance and necessity to carefully monitor rate of progression, both functional and structural, in patients with newly diagnosed disease.

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city of Toronto. He is Director of the Glaucoma Research Unit, Toronto Western Research Institute and a Senior Scientist at the Toronto Western Hospital. He is also the President of the Optometric Glaucoma Society.

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3 | New Thoughts on Tonometry and Intraocular Pressure

David Pye, MOptom

Intraocular pressure (IOP) is a risk factor for the development of glaucoma though the condition may develop at any IOP pressure level. IOP is the only modifiable risk factor and is determined by the amount of aqueous humor produced along with trabecular outflow, uveoscleral outflow and episcleral venous pressure. IOP shows greater variability in individuals with glaucoma, with IOP variation correlated with higher mean pressures, but there is independent risk factor. IOP is higher in individuals in the supine position, and often peaks just before awakening.

Prior to the 2007 ARVO meeting, the 4th Global World Glaucoma Association consensus meeting on IOP was conducted. The emphasis was placed on evidence based research, and the topic areas included the basic science of IOP, measurement of IOP as a risk factor for glaucoma development and progression, epidemiology of IOP, clinical trials and IOP, and target IOP in clinical practice. The highlights of the meeting are available from the World Glaucoma Association website: www.e-igr.com/MR/index.php?issue=91&MRid=188. Anyone who is seriously interested in the topic of the current status of IOP and its measurement, the book containing the discussion and consensus statements published by Kugler Publications is recommended.

During the year more papers, both theoretical and clinical in nature, have appeared which discuss the potential influence of central corneal thickness (CCT) and the biomechanical behavior of the cornea on IOP measurement. However, there is still no specific algorithm which would correct Goldmann applanation tonometry (GAT) readings for these aspects of the cornea and, as a result, some authors are recommending that pachymetry findings be used to classify corneas as thin, normal or thick rather than using a specific CCT correction nomogram for GAT. This then leads to two approaches to attempting to measure the true IOP, and a considerable number of papers have been published investigating both techniques.

One technique is to try to measure the biomechanical behavior of the cornea and make an allowance for these material properties to

better determine the IOP, and the second is to develop a method of tonometry which directly measures the IOP by overcoming the biomechanical influences of the cornea.

The Reichert Ocular Response Analyzer (ORA) is a non-contact tonometer which measures the time delay between the initial applanation measurement as a result of the puff of air and the second applanation which occurs as the cornea begins to regain its shape as a result of the topographical change produced by the initial stimulus. The instrument provides a measure of the corneal behavior, a Goldmann equivalent IOP (IOPg) and a "corrected" IOP (IOPcc) measurement as a result.

Measurements of corneal behavior taken with the ORA are called corneal hysteresis (CH) and corneal resistance factor (CRF). A number of papers have been published during the year attempting to relate corneal hysteresis (CH), in particular, to corneal disease and varying forms of glaucoma. Some of these studies suggest that CH may be useful in differentiating between patients with and without primary open-angle glaucoma. It is anticipated that a new version of the ORA software will be released soon which will improve the ease of use, a greater analysis of the waveform obtained and provide a quality index.

The Pascal tonometer (Dynamic Contour Tonometry or DCT) has a tip with a surface contour which resembles the corneal contour when the pressure on both sides of the probe tip is equal (Figure 1). When this occurs, the biomechanical effects of the cornea on IOP are significantly reduced, if not eliminated, and the small pressure sensor located in the probe tip provides an accurate measure of the IOP. There is a considerable amount of literature which suggests that the Pascal is less affected by corneal properties than GAT, although Kotecha et al reported that DCT IOP changes during the day were related to changes in CCT, but there was inter-subject variability.

Boehm et al reported on a prospective trial involving 75 eyes of 75 patients who were examined prior to undergoing phacoemulsification. Prior to phacoemulsification, the anterior chamber was cannulated and a closed system was utilized to set the IOP within the eye to 15, 20 or 35 mmHg. IOP measurements were then taken with a hand held Pascal device and compared to the intracameral measurements. The authors claimed that the results with the Pascal tonometer demonstrated good concordance with intracameral IOP measurements.

New tonometers such as the ICare seem to perform similarly to GAT, and other forms of tonometry using acoustic or infra-red technologies may appear in the future.



Figure 1. The Pascal Dynamic Contour Tonometer is seen with a measurement being taken. The IOP is displayed in the digital display.

In 2004, Leonardi et al published a paper which discussed the development of a contact lens device which could be worn to continuously measure IOP. Devices which monitor blood pressure and heart rate, and more recently blood sugar levels, over a 24 hour period are now available. There is some suggestion that a contact lens device based on the Leonardi et al principle may be available in the near future. This presents the interesting concept of being able to monitor the IOP of patients at frequent intervals

throughout the day and night which should help with patient diagnosis and management.

It is still difficult to compare studies which have investigated the relative performance of different tonometers. Often the protocols vary, the statistical analyses are different and differing populations are used for the studies.

Another approach has been used to investigate the effects of changes in the biomechanical behavior of the cornea on GAT. Hamilton et al reported on the effects on GAT of corneal swelling produced by two hours of eye closure and thick soft contact lens wear. The results suggest that at low levels of corneal edema, the cornea becomes stiffer and that the GAT results may overestimate the true IOP. The clinical implications are twofold. One is that if patients wear contact lenses, an estimation of their IOP with GAT will be less affected by corneal material properties if the patient does not wear their contact lenses on the day of measurement. If this is not possible, trying to measure the IOP of the patient after the same period of contact lens wear at each visit may be appropriate. The second implication relates to the diurnal variation of IOP. On eye opening, the average CCT is thicker than it will be for the rest of the daytime, and the measured IOP with GAT is highest.

Interestingly, the CCT and IOP measured in this fashion reduce at a similar rate over the first two hours after eye opening, suggesting a link between the two results. The increase in CCT alone does not explain the increased GAT result, and the soft contact lens swelling suggest that some of the increased IOP measurement is due to stiffening of the corneal tissue. Half of the increased GAT measurement of IOP on eye opening may be a result of increased CCT and Young's modulus of the cornea. To reduce the corneal effects on IOP measurements obtained with GAT, it would be advisable to ensure that the measurements are taken after the patient has been awake with eyes open for at least two hours. The biomechanical behavior of the cornea has also been reported to be affected by age. Elsheikh et al have reported in vitro studies of human corneas which were subjected to relatively slow and rapid rates of corneal inflation in an attempt to imitate GAT and non-contact tonometry respectively. The results demonstrated that corneas became stiffer with age, and this stiffening could significantly affect GAT results, and may be a significant factor to consider when measuring the IOP of patients who have had UVA and riboflavin treatment, although Romppainen et al found the effects of this treatment to be relatively small in an in vitro model.

It is difficult to know what a single IOP measurement means, and how it should be interpreted, as there seems to be more we need to know and understand before a meaningful determination of IOP can be made. Whilst research into the measurement of the true IOP continues, IOP is still an important measurement in clinical practice.

However, recent papers by Choudhari et al and Sandhu et al remind us of the need to frequently calibrate our GAT instruments and how these errors in calibration may affect our IOP measurements. Choudhari et al performed calibration testing on 132 slit-lamp mounted GAT instruments and found only 1% to be within the manufacturer's recommended calibration error tolerance at all levels of testing. Even if one applied a greater tolerance of ± 2 mmHg, 30% of the instruments were faulty.

Even if one knows the calibration error, Sandhu et al demonstrated that the error is not linear, so that a 1mmHg calibration error gave a change in GAT of +1mmHg, a 3mmHg calibration error gave a +1.6mmHg measurement error and a 4mmHg calibration error gave a

+3.6mmHg measurement error.

These results would suggest that GAT instrument calibration should be conducted as the manufacturer suggests on a monthly basis, to try to ensure comparable measurements of IOP over time.

Mr David C Pye, MOptom, is Senior Lecturer and Clinic Director at the School of Optometry and Vision Science, University of New South Wales, Australia.

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4 | New Technologies in the Diagnosis and Management of Glaucoma

John G. Flanagan, PhD, MCOptom

The last decade has seen an explosion of new technologies that have begun to challenge our understanding of the structural and functional relationships in early glaucoma, while at the same time introducing potentially new standards of care. In this chapter, I will review several of the latest technologies and developments.

Methods for the non-invasive, objective, quantitative, structural assessment include scanning laser tomography and optical coherence tomography for the optic nerve (ON) and retinal nerve fiber layer (RNFL); and scanning laser polarimetry for exclusive RNFL analysis. All three technologies are reported to have excellent diagnostic performance in the detection of early glaucoma. These instruments are not meant for stand-alone use but rather support the clinical evalua-

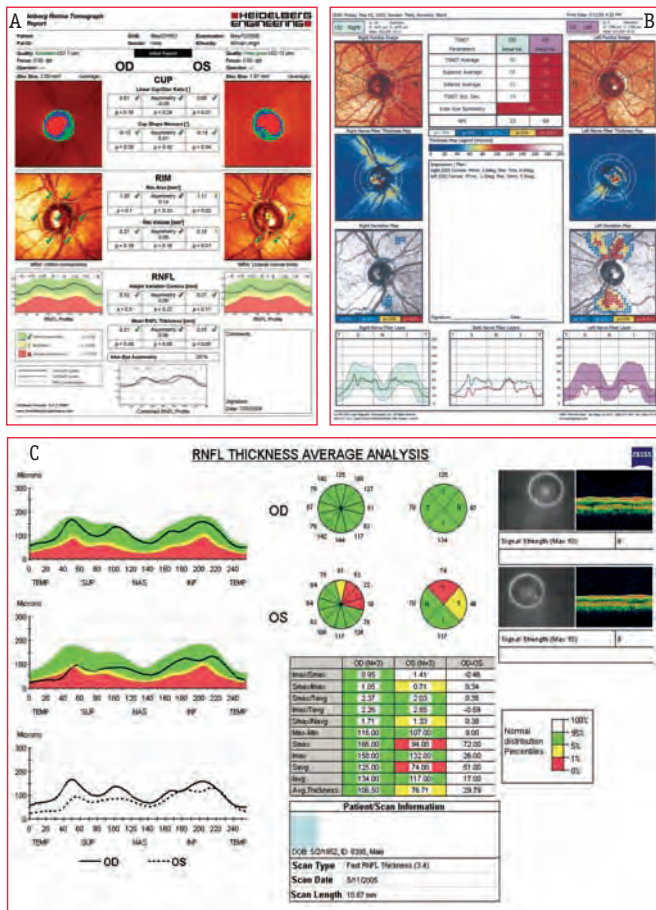


Figure 1a (top left), b (top right), c (bottom). HRT (a), GDX (b) and OCT (c) images of a patient with primary open-angle glaucoma. The loss is in the left eye only. All three technologies reveal the damage to be in the superior portion of the left optic nerve and retinal nerve fiber layer. This is seen as areas in the left eye that are flagged in the superior region. The GDX also shows loss in the inferior portion of the left eye, which does not correspond to the other tests or visual fields.

tion of the ON/RNFL. They may provide corroboration of a working diagnosis or require the clinician to re-evaluate his or her assessment of the ON/RNFL. They may also be used to follow for change over time.

Scanning laser tomographers (SLT) were first introduced in the late 1980's and are amongst the most common of the imaging systems for use in glaucoma. The technology is based on the optical principals of confocal microscopy. A series of images are recorded along the axial axis of the eye, thus enabling three-dimensional reconstruction of the surface of the retina and/or the optic nerve head. The Heidelberg Retina Tomograph (Heidelberg Engineering) is the most common of the SLTs (Figure 1a). The current, third-generation model, the HRT3, was introduced toward the end of 2005. The HRT3 is similar to the previous model in that

it operates using a 670nm diode laser light source and a field of view of 15x15 degrees, with a two-dimensional resolution for each image plane of 384 x 384 pixels. The scan depth is automatically selected from a range of 1.0 to 4.0 mm, and 16 scans are obtained per millimeter of scan depth. A 2-mm scan depth with 32 image scans has a one-second acquisition time (24msec per scan). The HRT3 offers several important developments over its predecessors. A sophisticated image acquisition quality control system has been incorporated. This reduces the learning curve for new users, and helps to ensure adequate image quality for future progression analysis. There is a new alignment algorithm that has reduced the intra-test variability, which in turn, enables more sensitive analysis of structural progression. The database for analysis of the stereometric parameters and Moorfields Regression Analysis (MRA) has been expanded to include 700 of Caucasian descent, 200 of African descent and 200 from Southeast Asia. This database is also used for the new, contour independent Glaucoma Probability Score (GPS), which is based upon automated analysis of the shape of both the optic nerve head and the parapapillary retina in both normal and glaucomatous eyes. The printout reflects these new measures and emphasizes the analysis of cup, rim, retinal nerve fiber layer and ocular asymmetry. There are additional improvements in the Topographic Change Analysis (TCA) that can now display graded levels of significance and Trend Analysis overview plots of cluster volume and area. The HRT was, until recently, the only imaging technology specifically designed to analyze progression, and has the added advantage of being backwardly compatible to its very first model. This means that some centers now have 17 years of consecutive data. The HRT has the ability to both align and analyze serial images. This is of particular importance as the greatest potential of the new imaging technologies lies in their detection of subtle structural changes early in the disease, rather than cross sectional classification and staging of the disease. Data from the ancillary study of the Ocular Hypertension Treatment Trial has indicated that baseline HRT measures were highly predictive for the development of POAG during the course of the study (MRA for the temporal inferior sector had a hazard ratio approaching 9.0).

Scanning laser polarimetry combines scanning laser ophthalmoscopy with polarimetry to measure the retardation of polarized laser light caused by the birefringent properties of the retinal nerve fiber layer (Figure 1b). The commercially available instrument is called

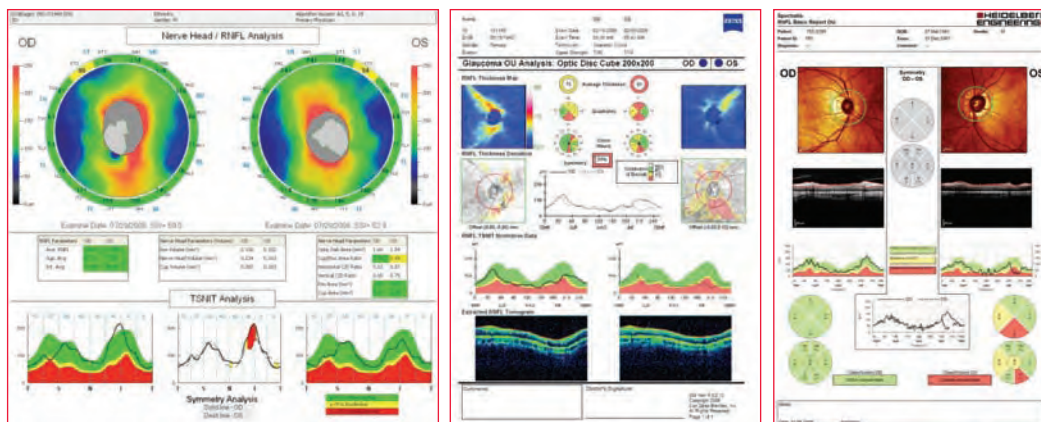


Figure 2: Glaucoma printouts for three of the new SD-OCTs. Left: The RTVue (Optovue Inc.) Center: Cirrus (Carl Zeiss Meditec) Right: Spectralis (Heidelberg Engineering). Note the common TSNIT plots.

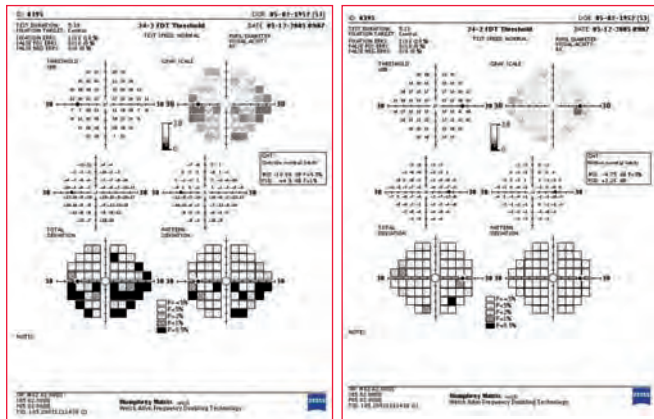


Figure 3a,b. These FDT Matrix 24-2 Full Threshold fields are from the patient seen in Figure 1. The right visual field is within normal limits, and the loss in the left correlates with the images in Figure 1 and SITA SWAP field in Figure 4.

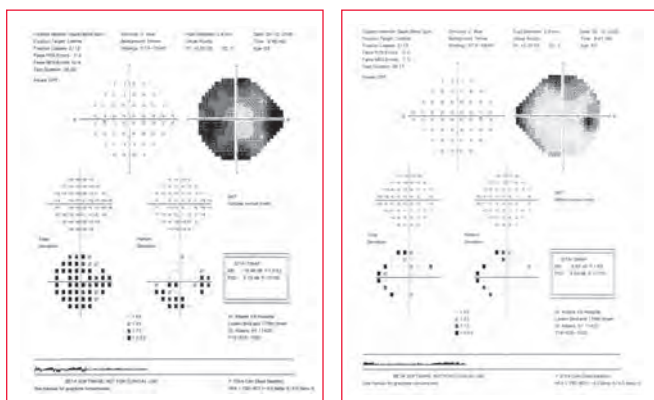


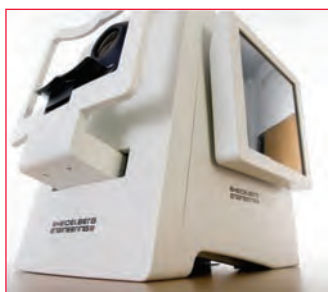
Figure 4. These are SITA SWAP fields for the patient seen in Figure 1 and 3. The loss is in the left eye, with the inferior points being flagged. The field in the right eye is consistent with a trial lens artifact.

the GDx VCC (Carl Zeiss Meditec), although the new GDxPRO will be available shortly. Like its predecessor, the PRO uses an 820nm diode laser source in which the state of polarization is modulated. Image acquisition takes 0.7 seconds and the scan field is 20 degrees. Results are compared to an age-matched normative database, and a machine classifier is used to define the likelihood that a map is normal or glaucomatous. Unlike the GDxVCC, the PRO uses Enhanced Corneal Compensation (ECC) algorithms with the idea of further reducing image noise and the effect of atypical scans. ECC is a sixth-generation approach, which like VCC employs individual specific compensation of the ocular birefringence but was developed to reduce the atypical “tie dye” appearance found in some lightly pigmented and myopic patients. Other new features of the GDxPRO include the evaluation of retinal nerve fiber layer integrity (RNFL-I). The idea being that unhealthy ganglion cells will cause disruption of the integrity of the RNFL and reduce the quality of the retardation image. There is also Glaucoma Progression Analysis (GPA) that enables the alignment and

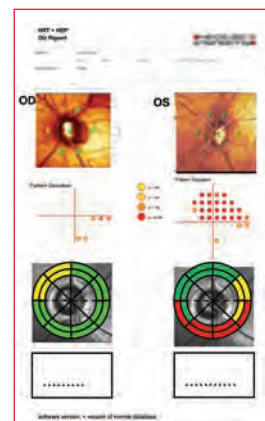
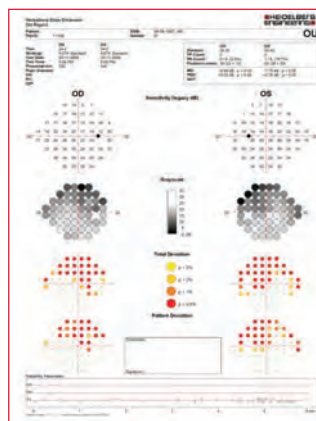
analysis of serial data. This is an important new feature, long missing in the GDx, permitting both trend and event-based analysis of disease progression.

Optical coherence tomography is the one technology that has changed exponentially with the introduction of high resolution, fourier or spectral domain (SD) OCT. Presently, the most commonly used of the OCTs is the Stratus OCT (Carl Zeiss Meditec) which is a third generation, time domain OCT that employs low-coherence interferometry to enable high-resolution, cross-sectional imaging of the retina and optic nerve. A superluminescent 830nm diode provides a near infrared, low-coherence source, which is divided and beamed to a reference device in the eye. Each light path goes back to a detector where the reference beam is compared to the measurement beam. The Stratus can be used in the diagnosis and management of glaucoma by measuring retinal nerve fiber layer (RNFL) thickness around the optic nerve head. Radial tomograms are then used to assess the cross-sectional profile of the optic nerve (Figure 1c). The OCT’s RNFL assessment correlates well with the clinical assessment of focal defects and visual fields in patients with glaucoma, and demonstrates a significant difference between normal and glaucomatous subjects. Results are compared to an age-matched normative database. A recent addition to the Stratus OCT is a GPA utility that illustrates potential change by overlaying serial thickness plots and performs linear regression on the average thickness data. The nature of time domain OCT means that it does not lend itself well to progression analysis, as serial alignment is uncertain. However it is both desirable and important to have even this rudimentary progression analysis.

SD-OCT was recently launched by nine different companies, including Optovue (RTVue), Heidelberg Engineering (Spectralis), Carl Zeiss Meditec (Cirrus) and Topcon (Figure 2). SD-OCT uses a stationary reference mirror, as opposed to the moving reference mirror found in time domain OCT. The interference between the sample and reference reflections are split into a spectrum and all wavelengths are simultaneously analyzed using a spectrometer. The resulting spectral interferogram is Fourier transformed to provide an axial scan at a fraction of the time previously required. This has resulted in up to a 100 times increase in the number of A-scans per second (Spectralis at 40,000 scans per second compared to the Stratus at 400 scans per second). In several of the new machines the OCT scans are paired with complimentary imaging modes, for example SLT, to enable registration of all A-scans. This allows image alignment of serial images, essential



5a (above). The Heidelberg Edge Perimeter (Heidelberg Engineering)
5b (center) OU printout of a HEP examination showing superior arcuate defects.
5c (right) OU Structure Function Map showing a matching borderline defect OD and an inferior defect of the ONH with an accompanying superior defect in the HEP field OS.



for the analysis of progression and overcoming the most significant problems associated with time domain OCT. The key to successful progression analysis is likely to be whether or not such images are acquired simultaneously with the OCT scans. If not, eye movements may remain a significant artifact. Glaucoma specific analyses are now available. The Cirrus, Spectralis and RT-Vue display RNFL maps and TSNIT plots of RNFL (Figure 2). In addition the RT-Vue segments the Ganglion Cell Complex (GCC), which comprises the RNFL, ganglion cell layer and inner plexiform layer, and currently displays the GCC in the macular region. The idea being that early glaucomatous damage is detectable in the macula. There are currently no published studies with respect to the diagnostic performance of the new glaucoma utilities. To date none of the manufacturers permit automated segmentation and analysis of three dimensional scans, undoubtedly the ultimate clinical tool.

New technologies for visual function have concentrated on selectively testing specific anatomical and/or perceptual pathways, so called Visual Function Specific Perimetry. The goal of such an approach is to detect loss of retinal ganglion cells (RGCs) earlier and with improved repeatability.

Frequency Doubling Technology perimetry (FDT) is based on the frequency-doubling illusion, whereby a low-spatial frequency grating (<1 cycle/degree) is flickered in counterphase at a high temporal frequency (>15Hz). When this occurs the spatial frequency of the grating appears to double. The technique has been applied clinically using a grating of 0.25 cycles/degree and temporal frequency of 25Hz. It was initially proposed that the illusion was due to selective processing of the My cells, a subset of magnocellular projecting RGCs. However, this is now thought unlikely, as there is no evidence for such cells in primates—although the illusion does preferentially stimulate the magnocellular system. It is likely that the stimulus, as used clinically, is a flicker contrast threshold task.

The original FDT tested up to 19 large, 10 degrees x 10 degrees targets in either a threshold mode or a rapid (<1 minute) screening test. During testing, the stimulus flicker and spatial frequency are held constant while the contrast is modified in a stepwise process similar to the bracketing method used in conventional perimetry. In response to concerns over the ability of such large targets to detect subtle, early defects, a second-generation machine was developed, the FDT Matrix, which uses smaller 5-degree targets and measures with a standard 24-2 pattern (Figure 3). A video camera is incorporated for fixation monitoring, and it is possible to view serial fields. A ZEST-like strategy is used to estimate the sensitivity and ensure a standardized test time, regardless of defect.

FDT has been reported to have high sensitivity and specificity for the detection of glaucoma. Even when used in the screening mode, it may detect some defects earlier than standard automated perimetry (SAP). FDT is relatively resistant to optical blur, small pupils and the influence of ambient illumination—all of which make it ideal in a screening environment. Recent reports on the Matrix suggest that it is capable of diagnosing early disease before SAP and often prior to SWAP. As disease progresses there is little difference with SAP results.

Short-wavelength automated perimetry (SWAP), or blue-yellow perimetry, uses a large Goldmann size V blue stimulus (centered on 440nm) against a bright yellow background (100 cd/m²) (Figure 4). The rationale is to selectively test the blue cones and their projection through the koniocellular pathway, thus taking advantage of their reduced redundancy. Several longitudinal studies found SWAP to be

predictive of early glaucomatous SAP visual field defect, in some cases by up to five years. SWAP is tested, analyzed and displayed in a way intuitively similar to SAP. SWAP is limited by the relatively greater influence of cataracts and other media opacities, a compressed dynamic range, poor test-retest characteristics and increased test time. The latter has improved since the introduction of SITA-SWAP. However, SWAP will probably not replace SAP and should be considered a complementary test to be used in selected situations, such as high-risk glaucoma suspects with normal SAP results.

Heidelberg Engineering is planning to launch a new visual function test called the Heidelberg Edge Perimeter (Figure 5). This is based upon an illusory stimulus called flicker defined form, in which a 5° stimulus region within a background of random dots is flickered in counterphase at a high temporal frequency (15Hz). The phase difference between the background dots and the stimulus dots gives rise to an illusory edge or border that is perceived as a circle or patch, against the mean luminance background. The stimulus targets the magnocellular projecting retinal ganglion cells and is proposed for the early detection of glaucomatous damage. HEP has been reported to have good test-retest repeatability and be capable of detecting early, pre-SAP glaucoma (figure 5c). Defects tend to be larger and deeper than those found using SAP. The HEP also features full range SAP, advised for use in neurological cases and advanced disease. Of particular note is the availability of the first ever combined Structure-Function Map, in which the HRT's MRA analysis is combined with the visual field analysis of the equivalent ON sectors (figure 5).

Current methods for the analysis of visual field progression include inspection of the Overview printout and the Glaucoma Progression Analysis (GPA), an updated version of the original Glaucoma Change Probability (GCP) analysis. Both are empirically based and compare a patient's pattern of change to "typical" change experienced by others with glaucoma. GCP was based on the total deviation plots, and was criticized for being prone to error in the presence of developing cataract and changing pupil size. The GPA was developed for the Early Manifest Glaucoma Treatment Trial (EMGT) and uses the pattern deviation plots, allowing an analysis that is less sensitive to the effects of cataract and reduced pupil size. GPA is available on the Humphrey Field Analyzer (HFA). The analysis uses estimates of the

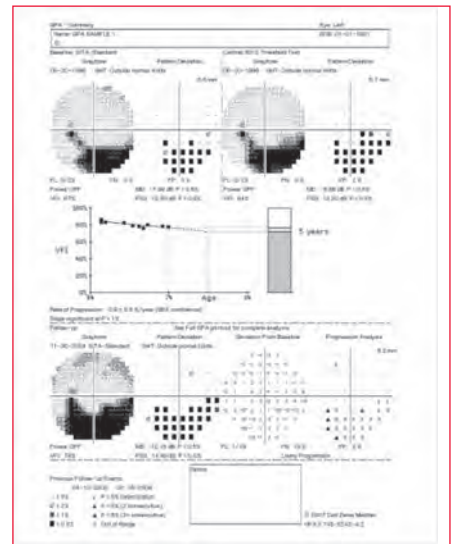


Figure 6: Glaucoma Progression Analysis summary printout showing a patient with slowly progressive glaucoma. The two fields at the top of the printout are the selected baseline fields; the center graph is the trend analysis for the Visual Field Index (87%) showing a slow rate of progression; the bottom field shows the most recent result. There is clear progression particularly in the inferior temporal region.

inherent variability of glaucomatous visual fields. This is combined with the EMGT criterion of three significantly deteriorating points repeated over three examinations. A minimum of two baseline and one follow-up examination are required. Each exam is compared to baseline and to the two prior visual fields. Points outside the 95th percentile for stability are highlighted, as are points that progress on two or three consecutive examinations. Two additional qualifying statements alert the clinician to the likelihood of “probable progression” (3x2 consecutive) and “likely progression” (3x3 consecutive). The Visual Field Index has recently been introduced and provides a method for the monitoring of rate of progression (see Chapter 2). The most recent version of GPA uses a single printout to illustrate the baseline fields, the VFI and its regression, and the most recent field with its GPA results (Figure 6).

New technologies have been developed and are gaining clinical acceptance. These new tests complement the examination and allow a better understanding of the visual field, optic nerve or retinal nerve fiber layer. The new technologies supplement tests we have been using for many years. As we gain better understanding of their use and strengths, they will only improve our ability to diagnose and manage glaucoma.

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5 | Risk Assessment as an Evolving Tool for Glaucoma Care

Robert D. Fechtner, MD, Albert S. Khouri, MD, and Murray Fingeret, OD

Whom should we treat? When? And how aggressively? The clinician treating patients with glaucoma or glaucoma suspects is faced with these challenging questions. Not all patients with glaucoma will lose vision to the extent that quality of life will be compromised. Our current model of diagnosing and treating glaucoma is based on

the principles of detecting damage, then lowering intraocular pressure to a level at which we believe the pressure-related component of damage will be reduced or eliminated. Then we follow the patient to monitor for progression. This model has obvious limitations. Early glaucoma is asymptomatic and difficult to detect. Only as the disease progresses are detectable structural and functional changes observed. Also, changes are irreversible and even a small achromatic visual field defect usually represents significant damage to the optic nerve.

We treat patients with ocular hypertension and glaucoma by reducing intraocular pressure (IOP). However, it is important to remember that the goal of glaucoma care is not to reduce IOP, not to preserve optic nerve and not to preserve visual field, but rather to preserve sufficient vision for acceptable quality of life. It is the loss of vision from glaucoma that impacts upon the quality of life for our patients. If our tools allow us only to base our treatment decisions on the degree of loss already present or on the detection of additional loss, we are missing an opportunity to identify and treat appropriately patients at greatest risk for losing vision before additional damage occurs.

Risk assessment is a well-accepted tool in other fields of medicine. Perhaps the best known example is cardiovascular medicine. Most adults are at least aware that elevated blood pressure and abnormal blood lipid profile increase the risk of coronary heart disease (CHD). Many have had blood pressure measured and a lipid profile tested. Risk assessment and modification is the fundamental tool for preventing coronary heart disease. No one wishes to learn of their risk by having the first heart attack! True, the consequence of gradual atherosclerosis is a cardiovascular event—quite dramatic compared with the chronic optic neuropathy and gradual loss of vision of glaucoma—but there are some parallels in the underlying principles of risk assessment. We can use the example of cholesterol.

The understanding of “cholesterol” as a risk factor has dramatically evolved over time. Early in the evolution of risk assessment for CHD, cholesterol was identified as a risk factor. Initially, normal cholesterol levels were defined as being within two standard deviations (SDs) of the mean (200 mg/dL to 310 mg/dL). Later, it was appreciated that there was a continuous effect, even within normal ranges. It soon became evident that subjects with the “normal range” of cholesterol levels included an excessively high incidence of CHD. In fact, the correlation between cholesterol levels and CHD occurred in a continuous, graded fashion, and normal cholesterol levels were still associated with increased risk of CHD.

The understanding of elevated IOP as a risk factor is analogous. Originally, abnormal IOP was described as two standard deviations from the mean (21 mmHg). We have subsequently learned that IOP is a continuous risk factor, even at statistically normal levels. Further, it is clear that one can have high IOP without glaucoma and one can have glaucoma with statistically normal IOP.

With the emerging evidence from large, prospective glaucoma trials, we are beginning to amass the data to allow us to be able to identify risk factors for both the development and the progression of glaucoma. Models allow the creation of risk calculators, tools to estimate individual rather than population risk. We can then determine who is at greatest risk. This can lead to better decisions regarding earlier or more aggressive intervention.

The results of recent large-scale trials have encouraged a reassessment of the way clinicians evaluate and manage patients with ocular hypertension (OHT) or glaucoma. The potential benefits of IOP



Figure 1. The Discoveries in Sight risk calculator, available on the Internet at www.discoveriesinsight.org.

reduction have been clearly demonstrated. The Ocular Hypertension Treatment Study (OHTS) investigated the effect of lowering IOP on progression to open-angle glaucoma (OAG) in over 1600 subjects with OHT but no evidence of glaucomatous damage. Treatment with topical ocular-hypotensive medication reduced the risk of progression to glaucoma by approximately half, from 9.5% in untreated patients to 4.4% in patients receiving treatment. A similar study, the European Glaucoma Prevention Study (EGPS), found no benefit from treatment of ocular hypertension with dorzolamide compared with placebo (vehicle of dorzolamide). However, the IOP reduction in the placebo group in EGPS was nearly the same as that in the dorzolamide treated group, a curious finding that has not been fully explained.

In the Early Manifest Glaucoma Trial (EMGT), subjects with newly diagnosed early glaucoma were randomized to either treatment or observation. This study demonstrated a benefit from treatment. IOP reduction slowed the rate of progression from 62% in controls to 45% in the treated population (median follow-up of six years).

For most clinicians, it is not surprising to get confirmation that lowering IOP prevents or delays the progression from OHT to glaucoma or from glaucoma to further visual field loss. Despite these encouraging findings, individualizing therapy based on the results from large-scale clinical trials is difficult. Although IOP reduction may decrease risk of glaucoma and vision loss, treatment costs and potential side effects also need to be considered. It would be helpful to know who is at greatest risk and most likely to benefit from treatment.

Perhaps more important than the clear demonstration of the benefits of IOP lowering in these studies was the identification of risk factors for the development or progression of glaucomatous damage. Several risk factors were identified at baseline in OHTS for the group who developed glaucoma. Older age was associated with increased risk of developing the disease over the course of the 5-year study. Despite this correlation, it is important to remember that glaucoma takes many years to progress to visual loss. Although increasing age is a risk factor, younger patients should have frequent eye exams since they have a greater remaining life span over which to develop vision loss. Higher untreated IOP in OHTS was also associated with a greater frequency of developing glaucoma. This is not surprising since IOP is a consistent risk factor in many studies. Patients with a greater cup-to-disc diameter (a measure of optic nerve damage) were more likely to develop glaucoma. It is not clear if some of the subjects with the larger cup-to-disc diameters already had early glaucoma without demonstrable visual field defects when they entered the study. In another analysis of OHTS data, optic disc hemorrhages were associated with a six-fold increase (95% CI 3.6-10.1; $p < 0.001$) in risk of

developing POAG in ocular hypertensive subjects.

An unanticipated observation from OHTS was that subjects with thinner corneas were at higher risk for glaucoma. While we know that the thickness of the cornea affects IOP measurements, this alone did not account for the increased risk. Thinner central corneal thickness was an independent risk factor. This has prompted clinicians to measure corneal thickness in patients with ocular hypertension and glaucoma on a routine basis.

The EMGT study identified factors for the progression of glaucoma in newly diagnosed patients. Risk factors present at the baseline visit that predicted who would progress included higher IOP, eligibility in both eyes (glaucoma in both eyes), presence of exfoliation material, worse visual field (mean defect) and older age. Once the patients returned for follow-up, additional factors that predicted progression included initial response to treatment (better initial response was protective), IOP at first visit and mean IOP at all follow-up visits, as well as percentage of visits at which a disc hemorrhage was detected.

In subsequent analysis of the Early Manifest Glaucoma Trial with a median follow-up of eight years the results confirmed earlier findings that elevated IOP is a strong factor for glaucoma progression, with a hazard ratio increasing by 11% for every 1 mmHg of higher IOP (95% confidence interval 1.06-1.17; $P < 0.0001$). Longer follow up (seven-11 years) from EMGT have refined our understanding of some of the risk factors. While level of IOP was an important risk factor, fluctuation of IOP was not an independent risk factor. A thinner central corneal thickness was a risk factor in those subjects with higher baseline IOP.

Recently, ocular perfusion pressure has been identified as a risk factor in both the EMGT study and the Barbados Eye Study. Perfusion pressure is defined as the blood pressure minus the IOP. It is not clear what cut-off indicates perfusion may be compromised. Still, the diastolic blood pressure may become an important factor in addition to the intraocular pressure as we evaluate risk in our glaucoma patients. This is a topic of considerable current interest. We will need to better understand the implications of these observations before we can integrate them into clinical practice. Blood pressure measurements may become part of glaucoma assessment in the future.

The OHTS publication included two 3x3 tables that included central corneal thickness and either IOP or C/D ratios. We could consider these as the first risk calculators. It was possible to combine two risk factors to derive an individual risk for the development of glaucoma. Steven Mansberger, MD, MPH, at Devers Eye Institute posted an interactive risk calculator based on the OHTS data on the internet at www.discoveriesinsight.org/GlaucomaRisk.htm (Figure 1). It has undergone modification since it was originally introduced. A version is available for download.

The first validated risk calculation model was published in 2005. This was also based on the OHTS risk model. The calculator was tested on an independent population of ocular hypertensive subjects followed at the University of California, San Diego. A cardboard "slide rule" and then a digital handheld risk calculator were produced. To be used precisely as designed, these calculators require input of data just as it was collected in the OHTS study. This data includes the age, intraocular pressure, central corneal thickness, vertical cup-to-disc ratio, pattern standard deviation (PSD) from a HFA II threshold visual field and diabetes status. However, in clinical practice a less stringent use should still provide reasonable estimates of risk.

More recently a risk calculator was developed by the OHTS study center (Figure 2). A prediction model was developed from the obser-

CONTINUOUS METHOD FOR ESTIMATING 5-YEAR RISK OF DEVELOPING POAG

INSTRUCTIONS:

1. Enter Patient Age and Ocular Data. (At least one measurement must be entered in each row.)
2. Click "Estimate Risk" to obtain the predicted 5-year risk of developing POAG.
3. Tooltips can be viewed by moving your mouse over any question mark.

FACTORS	RIGHT EYE MEASUREMENTS			LEFT EYE MEASUREMENTS		
	1 st	2 nd	3 rd	1 st	2 nd	3 rd
? Age <input type="text"/>						
? Untreated Intraocular Pressure (mm Hg) <input type="text"/>						
? Central Corneal Thickness (microns) <input type="text"/>						
? Vertical Cup to Disc Ratio by Contour <input type="text"/>						
? Pattern Standard Deviation Humphrey <input type="radio"/> Octopus loss variance <input type="radio"/>						

Estimate Risk Print Reset

Figure 2. The Ocular Hypertension Study and The European Glaucoma Prevention Study Glaucoma 5-year risk estimator is available at <http://ohts.wustl.edu/risk/calculator.html>. In this figure is the continuous method calculator. A point-system calculator is also available.

vation group of the OHTS that was then tested on the placebo group of the European Glaucoma Prevention Study (EGPS). A calculator to estimate the five-year risk of developing POAG, based on the pooled OHTS-EGPS predictive model, was found to have high precision in assisting clinicians deciding on the frequency of tests and examinations during follow-up and the advisability of initiating preventive treatment. The OHTS-EGPS calculator can be found online at <http://ohts.wustl.edu/risk/calculator.html>.

One question when the OHTS risk calculator was initially developed was whether to input diabetes status. OHTS found having diabetes to be protective of developing glaucoma but only diabetics without retinopathy were allowed into the study. Diabetes was not found to be a risk factor in the analysis of pooled OHTS-European Glaucoma Prevention Study dataset. Thus the influence of diabetes on the development of POAG remains questionable. A recent publication from OHTS, when the data were reevaluated after assessing the medical history, further found that diabetes was neither protective or a risk for glaucoma development.

How can a risk calculator add to the quality of clinical care? At the very least, we should better be able to determine whom to treat and whom to follow without treatment. It can be educational for the patient to demonstrate their risk status to explain treatment options and recommendations. One consensus group published suggestions that we should observe low-risk patients, consider treatment for moderate risk patients, and treat those at highest risk. The exact treatment threshold have not been clearly determined but this group selected ranges of <5% for low risk, 5-15% for moderate risk, and >15% for high risk. The rationale is that a glaucoma patient at highest risk to progress from OHT to glaucoma is also probably at relatively high risk for developing a glaucomatous visual disability in his of her lifetime. Other factors will also influence the decisions regarding treatment.

Risk calculators have not yet been developed for progression once a patient has glaucoma. But knowing the relevant risk factors can help us identify patients who might be at higher risk even if we cannot get a quantitative estimate of that risk. For now, we should evaluate our patients for known or suspected risk factors and either test for progression more frequently or treat more aggressively those we consider at higher risk.

Can we predict which glaucoma patient is at risk for progressing

and ultimately developing a visual disability? OHTS identified risk factors for the progression from OHT to open-angle glaucoma (OAG). Risk calculators are now available to help the clinician estimate individual risk of progression. The EMGT and other studies identified some of the risk factors for progression of OAG. As we refine models of risk, we will better be able to determine which patients are at highest risk and may need aggressive treatment. Conversely, we should identify patients at low risk who can be followed closely without treatment. This requires a fundamental change in our view of glaucoma treatment. Rather than think of it simply as IOP-lowering treatment, we might start to consider it as risk reduction. Of course, we must consider patient preferences and views about risk in making these determinations.

Well-designed clinical trials in glaucoma will continue to advance our understanding of the spectrum of this disease. It is not only reassuring that many of our cherished traditions are now supported by evidence, but also intriguing to explore new concepts about glaucoma based on large, well-designed studies. At first, we will make qualitative determinations by identifying risk factors in our patients and altering our treatment decisions. Eventually, we can expect to have risk calculators as tools to help decide whom to treat, when to treat and to what extent.

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6 | Understanding IOP Lowering Medications

Murray Fingeret, OD

Medical therapy is the most common method used for the reduction of the intraocular pressure (IOP) associated with ocular hypertension (OHT) and open-angle glaucoma (OAG). Several classes of drugs (prostaglandin derivatives, beta-adrenergic antagonists, carbonic anhydrase inhibitors, adrenergic agonists and cholinergic agonists) may be used to reduce the IOP. Medications may be classified in several ways: their mechanism of action, efficacy, safety, tolerability and patient acceptance. Mechanism refers to what receptor is stimulated or blocked as the drug achieves its effect. Efficacy refers to how well the medication reduces IOP, both in the short- and long-term. What is the drug's response rate? For example, how many individuals will have their IOP reduced from the baseline level by 15%, 20%, 25%, 30% or more? How often will the IOP creep back towards pre-treatment levels months to years later? Tolerability refers to how well the drug is tolerated and accepted. How often does the patient or doctor feel that side effects preclude continuing the medication? In the perfect world, the clinician would like to select an agent that shows excellent efficacy and persistency, as well as being safe and well-tolerated.

Cholinergic agents, such as pilocarpine, were the most commonly used agent to treat open angle glaucoma until the introduction of timolol. In 1978, beta-adrenergic antagonists were introduced and soon thereafter became the drug of choice. Their popularity stemmed from improved efficacy, a reduced dosing schedule and favorable side effect profile. Over the next two decades, other drug classes (topical carbonic anhydrase inhibitors, adrenergic agonists, cholinergic agents) became available to complement beta-adrenergic blockers. During this period, several adrenergic agonists (epinephrine, dipivefrin) became obsolete as newer drugs with significant advantages came to market. In 1996, a further evolution occurred with the introduction of prostaglandins (PGs). The first PG introduced, latanoprost (Xalatan), soon replaced beta-adrenergic blockers such as timolol, as the primary agent to lower IOP in ocular hypertension and glaucoma. With the use of PGs, IOPs once obtainable with multiple medications

were within reach using a single agent. In addition, compliance improved and diurnal IOP variation was reduced.

Beta-adrenergic antagonists were introduced in 1978 with timolol maleate. Since then, additional beta-adrenergic antagonists include levobunolol, betaxolol, metipranolol and carteolol. Betaxolol is different from other medications in this class in that it is a cardio-selective agent that primarily blocks beta1 adrenergic receptors. Carteolol is also unique in that in addition to being a nonselective beta-adrenergic antagonist has intrinsic sympathomimetic activity (ISA). Nonselective adrenergic antagonists are available in both solution and gel formulations. A gel formulation increases the drug's contact time, enhances efficacy and reduces systemic absorption but is usually uncomfortable. Istalol is a specific formulation of timolol maleate that increases the drug's penetration into the eye, allowing it to be used once per day. The beta-adrenergic antagonists reduce IOP between 22 -28% by inhibiting the production of aqueous humor. The nonresponder rate is approximately 20%. While the dosage for solutions is listed as bid, the nighttime dosage has little impact on IOP reduction. The morning instillation is the more important for the patient to perform. Topically, the drugs are well-tolerated. The larger concern with the use of topical adrenergic antagonists is their systemic absorption and potential side effects. Side effects include confusion, lethargy, fatigue, bronchospasm and bradycardia. While beta-adrenergic blockers appear to be safe as long as patients with known contraindications (such as pulmonary conditions) avoid them, their use nonetheless has declined over the past decade with the introduction of PGs. PGs have less systemic side effects than beta blockers and a better dosing schedule. Also, oral adrenergic antagonists are used by internists and cardiologists to treat many cardiovascular conditions. When given systemically, they often reduce the IOP, minimizing the impact if a topical beta blocker is also utilized. In most situations when patients requiring IOP reduction are on oral beta-adrenergic antagonists, PGs become the drug of choice. Still, one advantage of this drug class is that drugs such as timolol or levobunolol are available as generics, which are less expensive than branded medications.

Apraclonidine (Iopidine) was the first drug in a class known as adrenergic agonists. Brimonidine (Alphagan, Alphagan P) is the other member of this category and the most commonly used drug in this class. Adrenergic agonists inhibit the production of aqueous humor and enhance outflow mechanisms, which leads to an IOP reduction of 22% to 28%. Several side effects occur with apraclonidine including the development of an allergic follicular conjunctivitis and loss of effect over time (tachyphylaxis). Brimonidine is affected to some extent by these same side effects but has replaced apraclonidine as the adrenergic agonist of choice. One important difference between adrenergic agonists and beta-adrenergic antagonists is the duration of action. The short duration of action of adrenergic agonists requires that they be used on a tid dosage when they are the only medication utilized. This peak-and-trough effect associated with adrenergic agonists is one reason why they are commonly used in a secondary role. When used in conjunction with other agents, they can be used on a bid basis. Brimonidine is available in a branded product (Alphagan P, 0.10%, 0.15%) and a generic formulation (0.2%). Adrenergic agonists are relatively safe medications, though they should not be used in children due to concerns regarding lethargy. Other side effects include dry mouth, fatigue and drowsiness. Brimonidine 0.2% along with Timolol 0.5% makes up the fixed-

combination product Combigan, and is a bid agent. The indication for this medication is when additional IOP reduction is needed. It is not typically used as a first line agent but rather run in after one of the drugs components is tried found to be safe and effective but additional IOP lowering is desired.

Topical carbonic anhydrase inhibitors (CAI) inhibit the production of aqueous humor and reduce the IOP by 16% to 22%. They work by inhibiting the enzyme carbonic anhydrase in the ciliary processes of the eye. Originally, CAIs were available only in an oral form (acetazolamide, methazolamide) and were known to induce systemic side effects, such as paresthesias, depression, diarrhea, metallic taste, kidney stones and aplastic anemia. Because CAIs reduce IOP so effectively, a topical formulation was developed. With topical preparations, the inhibition of the carbonic anhydrase enzyme is limited to the eye, dramatically reducing systemic side effects. Dorzolamide 2% (Trusopt) solution was the original drug in this class, followed by brinzolamide 1% (Azopt) suspension. These topical formulations have been shown to be safe, with the most common side effects being local irritation such as burning and stinging (more pronounced with dorzolamide). However, one concern is that the drugs are from the sulfa family and are therefore contraindicated in individuals with sulfa allergies. CAIs are rarely a primary medication and are almost always used with other agents. Topical CAIs are quite effective when employed in combination with other agents. When combined with timolol to produce Cosopt (timolol-dorzolamide), which is used twice per day. CoSopt has recently become available generically. Topical CAIs are an excellent secondary agent, used when the individual's primary drug is effective and tolerated but further IOP reduction is needed.

Cholinergic agents reduce the IOP by causing the ciliary muscle to contract, leading to improved flow through the trabecular meshwork. Pilocarpine is the most common of the agents making up this class and is available in concentrations ranging from 0.5% to 12%. The most frequently used strengths are 1%, 2% and 4%. Pilocarpine is used infrequently due to its qid dosing schedule and commonly induced local side effects including browache, dim vision, blurred vision and headache. It is a safe drug systemically and can reduce IOP up to 25%.

The introduction of timolol led to a quiet revolution in the way glaucoma was managed. Therapy went from an irritating, difficult-to-tolerate agent (pilocarpine) to one that was well-tolerated and effective (timolol). A further revolution occurred in 1996 with the introduction of latanoprost (Xalatan). Dosage was reduced to once per day, IOP reduction enhanced (26% to 34%) and systemic and local side effects reduced. The increase in uveoscleral outflow is caused by the elevated presence of metalloproteinases, which break down the collagen matrix within the uveoscleral region that surrounds the ciliary muscle bundles. New channels for aqueous outflow are created, boosting uveoscleral outflow to greater than 50% of total flow from the eye. Since the introduction of latanoprost, additional PGs have become available including bimatoprost (Lumigan) and travoprost (Travatan). Both latanoprost and bimatoprost are listed on the drug's package insert as capable of being a primary agent. PGs have a long duration of action, allowing them to be used once per day while maintaining a flattened diurnal curve throughout a 24-hour period. If needed, other glaucoma agents may be added to PGs. Tachyphylaxis and systemic side effects are rare with local side effects while irritating, not serious. Hyperemia is the most common

side effect and is seen least commonly with latanoprost, followed by travoprost, with bimatoprost causing hyperemia most often. Other side effects include iris darkening, which is most commonly seen in individuals with mixed-colored iris, periorbital skin darkening, eyelash growth, anterior uveitis, cystoid macula edema (CME) and irritation. Travatan Z is a newer formulation of travoprost, with Sofzia being used as the preservative instead of benzalkonium chloride (BAK). The intent with the introduction of a non-BAK preserved solution is to reduce symptoms that may be associated with chronic BAK use. CME and anterior uveitis are rare and, when present, almost always occur in eyes with a risk factor such as prior intraocular surgery or a history of iritis. Eyelash growth is reasonably common, but fortunately is only a cosmetic concern. The iris color change is caused by an increase in the size and number of melanin granules within the iris stromal melanocytes. The pigment is contained within the iris, and no signs of increased pigmentation are seen anywhere else in the eye. Periorbital skin darkening is another commonly encountered side effect that typically disappears upon discontinuation of the agent.

There has been controversy as to which of the PGs most effectively reduces IOP. Well-conducted studies provide conflicting results. For example, the XLT study evaluated the three PGs and showed that they were comparable in efficacy, while hyperemia was most common with bimatoprost. A meta-analysis published by van der Valk et al also showed PGs to be similar in efficacy. In a study performed by Noecker, Bimatoprost showed slightly greater efficacy along with increased side effects. Another area of question is whether switching PGs within the class is an effective strategy. There are several reasons why a PG may not be effective in a particular patient. Different studies have shown that approximately 9% of individuals will show <15% IOP reduction when any of the PGs are utilized. Will switching from one PG to another lead to a greater IOP drop? Possibly, but the studies used to evaluate this question are confusing. Switch studies have shown that no matter what the first or second drug is, IOPs will be lower on the second drug. Reasons why the IOP may be reduced include improved compliance or a phenomenon called regression to the mean. Regression to the mean describes the situation in which it takes several IOP readings (data points) to know what the true IOP range is throughout the day (diurnal variation). Whether a switch within class lowers IOP over the long term is still open to question. It may reasonable to switch within class to obtain lower IOPs but the clinician should understand that short term IOP reduction may not be achieved in the long term. Still, if a person is experiencing side effects with one PG, switching to another is an advisable step in reducing these symptoms.

Fixed combination (FC) products include timolol 0.5%-dorzolamide 2% (CoSopt) and timolol 0.5%-brimonidine .2% (Combigan). Combigan is the first combination product approved by the FDA in 10 years. There are other fixed-combination products available throughout the world but the FDA has stringent requirements in regards to both IOP reduction and safety and only recently approved Combigan. FC products are typically used as adjunctive agents when further IOP reduction is required. These agents reduce the IOP additionally by approximately 20-25%. Both drugs mirror the side effect profile of their individual components. Surprisingly, the side effect profile for Combigan appears to be better than expected. One issue with brimonidine 0.2% was the development of allergic conjunctivitis which is lower with Combigan as compared to use of brimonidine alone.

The advantages of FC products are convenience (one drop instead of two), improved compliance, reduced exposure to preservatives and less chance of the second drop washing out the first. Approximately 40% of individuals on a PG require a second agent to achieve the target pressure. A drug such as brimonidine or dorzolamide may be then added to the PG to further reduce the IOP. If this agent is effective and tolerated but further IOP reduction is needed, the second agent is then discontinued and replaced with the fixed combination product. This allows two bottles to be used with three agents going into the eye to reduce IOP. While some clinicians may go directly to a fixed combination agent, this is not recommended since if either of the agents in the FC product is not effective or side effects occur, it may not be clear which agent is the culprit.

Glaucoma medications have evolved over time. We are now at a point where PGs have become the primary agent for therapy, and timolol is used less often in a primary role. Other agents, including FC products may be used to complement PGs, always with the aim of reducing the IOP to the needed target levels while keeping side effects to a minimum.

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7 | The Management of Glaucoma

Murray Fingeret, OD

There are many situations that confront the optometrist as he or she decides whether to initiate therapy for ocular hypertension (OHT) or glaucoma. For ocular hypertension, the decision process, which involves the concept of risk, is discussed in Chapter 5. In regard to glaucoma, when optic nerve and/or visual field damage associated with glaucoma is recognized, therapy is in order. The signs of glaucomatous damage are discussed in chapter 2. Before therapy

commences, a strategy is developed based upon the stage of disease, the person's age, IOP level, as well as other factors. A target intraocular pressure (IOP) range is determined and a medication selected. If therapy is not indicated, the patient is often classified as a glaucoma suspect and followed once to twice per year, depending upon the individual's characteristics. The category of glaucoma suspect includes individuals with ocular hypertension as well as suspicious optic nerves or visual fields.

When medical therapy is initiated, the selection for the initial agent usually comes from one of two classes of drugs: prostaglandins (PGs) or topical beta-blockers. Over the last decade, PGs have replaced beta-adrenergic antagonists as the most commonly used agent for initial therapy. This is due to their ability to reduce IOP efficiently on a once-per-dosage schedule, without inducing serious side effects, as well as their dampening IOP fluctuations that may occur over a 24-hour period (diurnal curve).

The initial medication selected is based upon its ability to reduce IOP, its safety profile, tolerability and patient acceptance. The drug needs to be matched to the patient. For example, a patient with a history of anterior uveitis or macula edema would not be a good candidate for PG therapy. Likewise, a patient with pulmonary disease would not be a candidate for beta-adrenergic antagonist therapy. Target IOPs must also be considered as a therapeutic agent is selected. Target pressures refer to the range of IOP that we hope will prevent further deterioration. A patient's target IOP may change over time, either as new knowledge becomes available indicating lower IOPs will be advantageous or if progression is confirmed. Target IOPs are a best guess of what IOP will control the condition. The best indicator to show that target IOP has been achieved is when periodic optic nerve and visual field evaluations reveal no change. If change is noted, additional reduction is necessary.

Target IOPs are based on the amount of damage present and the highest IOP reading, with greater reduction required as damage worsens. Recent clinical trials have provided evidence that lower target IOPs are important, though no study has shown exactly what IOPs are optimal. The Ocular Hypertension Treatment Study (OHTS), which had a target IOP reduction of 20%, found that 4.4% of individuals in the therapy group progressed. In a study of glaucoma patients, the Early Manifest Glaucoma Trial (EMGT), in which the average IOP reduction was 25%, 45% of patients in the therapy group progressed over time. The Collaborative Initial Glaucoma Treatment Study (CIGTS) which also used a group of patients with glaucoma monitored for progression. CIGTS found little change in the group whose IOP was reduced 38%. In the Advanced Glaucoma Intervention Study (AGIS), groups were broken down based on the percentage of visits in which the IOP was reduced below 18mmHg. One group with a mean IOP of 20.2mmHg showed significant deterioration while another group with a mean IOP of 12.3mmHg appeared to be stable over an eight-year period. These studies, taken as a whole, do not provide evidence that IOPs need to be reduced to the low teens for all patients, but they do illustrate the need to reduce IOPs to lower levels than previously thought.

The EMGT found risk factors associated with glaucomatous progression include higher IOP at the time of diagnosis, pseudoexfoliation, bilateral disease, disc hemorrhages, older age and worse visual field mean deviation. The AGIS found variation in IOP over a 24-hour period as an additional risk factor. This is a separate risk that describes IOP fluctuation throughout the day, even when IOP

is low at certain time points. To recognize diurnal fluctuations, one should record the time of each visit and schedule exams at varying times during the day.

Often it is helpful to begin therapy with a monocular or unilateral trial in which medication is begun in one eye for a few weeks, with the contralateral eye serving as a control. The rationale is that IOP, while often different between the two eyes, will rise and fall over the day to a similar degree. Also, the response to a medication should be similar in both eyes. Since non-responder rates vary from 8% to 25% depending on the class of medication, a monocular trial is one way to ensure the medication is effective as well as determine if side effects are occurring. Anthony Realini has, in a series of studies, questioned the use of the monocular trial. His rationale is that IOP reduction in one eye does not predict performance of the drug in other eye. Moreover, monocular trials require at least one additional visit. Nevertheless, many experts continue to recommend the monocular trial, recognizing its limitations but also using it as a way to control initiation of a new drug.

At the outset of therapy, the patient needs to be educated in regard to the optimal time for drop instillation(s) and potential side effects. It is important to demonstrate proper eyedrop instillation technique and have the patient demonstrate that he/she can properly instill the drops. If eyedrop instillation appears to be a problem, there are devices to aid instillation. Also, a companion or family member may aid in medication insertion. Finally, written dosing schedules should be provided as reminders. The first follow-up visit usually occurs two to four weeks after therapy commences. At each visit, ask if any side effects have occurred and when the patient last used the medication(s). Patient communication is discussed in Chapter 10. Even when written schedules are provided, some patients misunderstand how to use the medication. Questions that should be addressed at every visit include whether the patient is actually using the drug or if there are any problems or concerns. The IOP is measured to assess whether the medication is effective and IOP is at target level. If the drug is well-tolerated and effective, then the patient is followed over time, watching for medication side effects as well as progression. Patients are seen every three to six months depending on severity and type of disease. Ocular hypertensives are monitored less often and individuals with significant loss more often. Dilated optic nerve evaluation, imaging and visual field testing should be performed at least yearly. Testing more often is recommended if a greater degree of loss is present or a question of stability arises. Gonioscopy is usually performed every other year.

An important question that should be considered early in the course of follow-up is the rate of change. If a patient is progressing rapidly, this needs to be recognized and therapy modified. One way to measure rate of change is to perform perimetry on a six-month basis for the first two years. This is best done with SITA visual fields and the Glaucoma Progression Analysis (GPA) software tool. If the fields are unchanged, the interval between field testing can be increased to yearly. Approximately five fields are needed before a decision can be rendered regarding stability.

One challenge occurs when the IOP is not reduced adequately or side effects develop with the initial medication. If side effects occur, what are they? Are they caused by the medication? May they be reduced if a switch occurs within the same class of drugs? An intra-class switch may work if hyperemia develops with one PG. A more difficult question is if the target IOP level is not reached with

the initial medication. In this case, the IOP response needs to be evaluated. For example, if the IOP was very high and/or the damage significant, leading to a target goal of 40% reduction, and the drug provides 25% of the target reduction, then the medication appears to be effective, but a second agent is needed. On the other hand, if the actual reduction is 15% or less, the patient may be considered a non-responder. Inadequate responses do occur and are not often recognized, leading to unachieved target levels. We should ask if progression may occur in 15 years at the present IOP level. It may be then easier to appreciate the urgency of attempting to achieve target IOP levels.

There are different reasons why the IOP may not have been reduced with the initial agent, including lack of response or poor compliance with the clinician faced with a decision of how to proceed. Switching to a drug within the same class, such as going from one PG to another (intra-class switches) is controversial since it is not proven that such switches work. Switch studies with PGs have shown that the medication switched to always performs better. Also, most switch studies have been conducted over short periods, usually about 30 days which is not long enough to evaluate the response. The improved efficacy may be due to the second drug's greater response, but other possible reasons for the reduction include improved compliance or fluctuations in IOP (regression to the mean).

If the medication is effective but further reduction is needed, either because the IOP is above the target goal or progression is identified, the practitioner may choose an additional medication. If a PG is the initial agent, the second agent may be a beta-blocker, alpha agonist or topical CAI. A beta-blocker offers the convenience of once-per-day use; thus the patient would take it in the morning and take the PG at nighttime. Still, there is evidence that beta-blockers do not offer much additional IOP reduction when added to a PG. When added to a PG, topical CAIs or alpha agonists may be more effective at lowering IOP than beta-blockers but they require twice-per-day dosage. If a patient is on a PG along with a beta-blocker, alpha agonist or topical CAI and further IOP reduction is needed, then these drugs may be discontinued and a fixed-combination agent containing timolol-dorzolamide (Cosopt) or timolol-brimonidine (Combigan) begun. It is important to stress to patients taking two medications that they should wait five minutes before instilling the second agent to avoid washing the first from the eye. Also, remember to instruct patients taking beta-blockers to close their eyes or occlude their punctum for three minutes. This will reduce systemic absorption, improve efficacy and reduce side effects. Argon or Selective Laser Trabeculoplasty and filter surgery become options when the patient is progressing or the IOP is above the target level, and several medical options have been tried (see Chapter 8).

In some cases, even with patients who respond well to initial therapy, the IOP may slowly rise over time (long-term drift). Such increases could be due to the glaucoma worsening, problems with compliance or the development of tachyphylaxis. The two questions to ask are: is the drug effective, and is it being used? If the IOP is elevated, instill the medication and measure the IOP one-two hours later. Also, observe the patient's drop instillation technique to determine if the drug is getting into the eye. And finally, the reverse monocular trial may be helpful to address whether tachyphylaxis has developed. In this trial, the drug is temporarily discontinued in one eye and continued in the other. If tolerance has developed, there will be little change in the untreated eye's IOP over the next several

weeks. However, a rising IOP proves the drug is effective and should be continued, but an additional agent is necessary.

The management of ocular hypertension and glaucoma is an art that requires the clinician to make an ongoing series of decisions and adjustments over the patient's lifetime to ensure the IOP remains at acceptable levels and the condition does not worsen. Periodic monitoring of the optic nerve, retinal nerve fiber layer and visual fields are also necessary. The doctor needs to consider both the short and long-term view to ensure stability occurs throughout the lifetime of their patient.

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8 | When Medical Therapy Fails: Surgical Options for Glaucoma Management

Kathy Yang-Williams, OD

Surgical intervention becomes an option in the management of open-angle glaucoma when the intraocular pressure (IOP) cannot be sufficiently reduced with medical or laser therapy to prevent progressive optic nerve damage and/or visual field loss. Surgery should also be considered when medical treatment is unavailable, the patient cannot adhere to the treatment regimen or the cost of medical therapy exceeds their means. Consideration for surgical intervention should include disease severity, advanced optic nerve damage or visual field defects with threat to central vision, and the age and systemic status of the patient.

Selective laser trabeculoplasty (SLT) is a newer procedure performed with a Q-switched 532nm Nd:YAG laser to reduce IOP (Lumenis Inc, Santa Clara CA). SLT may cause less collateral damage than argon (ALT) or Diode laser trabeculoplasty as it "selectively" targets the pigment-containing cells in the trabecular meshwork (TM) using a larger spot size, lower power setting and less total energy than ALT or diode. As compared to ALT, SLT creates less thermal damage to the trabecular meshwork, less post-operative pain and inflammation, and is less dependent on pigmentation of the angle. The potential

for repeat procedures has been proposed as a possible advantage to SLT with a recent retrospective case series demonstrating further IOP reduction with repeat 360° SLT as early as 6 months following loss of efficacy from the initial SLT procedure. The IOP reduction from any form of laser trabeculoplasty is generally equivalent. The IOP decline is typically not permanent, with IOP often rising to pre-treatment levels over a few years. New laser techniques include the 790 nm titanium: sapphire laser (TiSaLT by SOLX Inc., Waltham MA) which has been shown to be comparable to ALT as well as micropulse laser trabeculoplasty (MLT) which utilizes an 810 nm diode laser to prevent cellular destruction as occurs in ALT (IQ 810, Iridex, Mountain View, CA).

Glaucoma filtering surgery is intended to provide long-term control of IOP without medications and to maintain adequate diurnal control with minimal post-operative complications or subjective discomfort. The current gold standard for glaucoma filtering surgery is the trabeculectomy with adjunctive anti-fibrotic agents applied intraoperatively or injected postoperatively (e.g. mitomycin-C [MMC], 5-fluorouracil [5-FU]). Trabeculectomy (guarded scleral fistulization), was first popularized by Cairns in 1968. Trabeculectomy remains associated with a number of complications including bleb dysesthesia (symptomatic bleb), cataract, bleb failure, hyphema, wound leak, flat anterior chamber, ocular hypotony, hypotony maculopathy, choroidal detachment, suprachoroidal hemorrhage, bleb infection, and endophthalmitis. Surgical variations of this procedure have been designed to reduce the frequency of these complications. The use of anti-fibrotics reduces the risk for bleb failure by repressing the formation of scar tissue at the surgical site but may lead to ischemic filtration blebs vulnerable to leak and late infection.

Anti-metabolites are indicated for high-risk patients, such as younger patients, those with a history of failed filtration surgery, African-Americans and individuals with aphakic, uveitic, neovascular or secondary angle closure glaucoma. One concern is that anti-metabolites, particularly mitomycin, have been associated with a higher risk for late wound leak, blebitis and endophthalmitis. Patients may present initially with an infected bleb, or "blebitis," associated with a painful red eye, photophobia and discharge. If the infection extends into the eye (bleb-associated endophthalmitis), significant anterior chamber reaction or hypopyon can result. Even with aggressive antibiotic treatment, the prognosis for patients with bleb-associated endophthalmitis is poor. Trabeculectomy is a well-established technique but poses significant risk for early and late post-operative complications. Frequent post-operative visits are necessary and additional interventions may be required to ensure the success of the procedure. Even with adjunctive anti-fibrotics, up to 50% of trabeculectomies fail by five years.

The FDA approved Ex-PRESS mini glaucoma shunt is a procedure similar to trabeculectomy initially; however, no peripheral iridectomy is required (Optonol Inc, Kansas City, KS). Instead, a 3mm long, non-valved stainless-steel implant (usually with an internal diameter of 50µ) is placed under a partial thickness flap [Figure 1]. Originally, the Ex-PRESS shunt was placed under the conjunctiva alone but this was accompanied by a high incidence of extrusion, hypotony and related complications. A revised technique places the device underneath a scleral flap and utilizes intraoperative mitomycin. A retrospective study comparing the Ex-PRESS to standard trabeculectomy reported the Ex-PRESS implant under a scleral flap had similar IOP-lowering efficacy with a lower rate of early

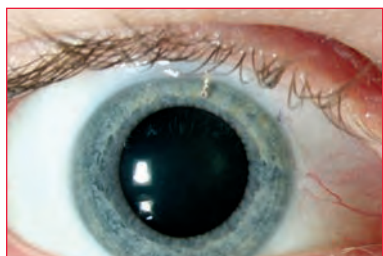


Figure 1. Ex-PRESS mini glaucoma shunt. (Courtesy of Dr. Rouwen, Netherlands)

hypotony compared with trabeculectomy. A recent prospective, randomized trial found better success with the Ex-PRESS shunt compared to trabeculectomy and similar rates of post-operative complications and interventions. An additional comparative case series of 345 eyes (241 Ex-PRESS alone and 114 Ex-PRESS combined with cataract surgery) with follow-up of 3 years reported 94.8% success for the Ex-PRESS implant only group, and 95.6% for the combined group (IOP \leq 21mmHg with or without medications). The most common device-related complication was obstruction of the tube in 6 eyes (1.7%), which was treated successfully with Nd:YAG laser in all 6 eyes. Longer term complication rates related to the device or bleb formation are yet unknown.

Non-penetrating glaucoma surgeries (such as viscocanalostomy and deep sclerectomy with or without collagen implant) reduce the risk of flat anterior chamber in the immediate post-operative period by creating an alternative outflow pathway without the anterior chamber being penetrated as occurs in trabeculectomy. Non-penetrating glaucoma surgeries do not usually result in the formation of a filtering bleb and if a bleb develops post-operatively, it tends to be more shallow and diffuse than that observed following trabeculectomy. However, studies evaluating non-penetrating glaucoma surgery show that intraocular pressure reduction is generally not as great as that achieved with trabeculectomy. If further IOP reduction becomes necessary, laser goniopuncture can convert a non-penetrating glaucoma surgery to a penetrating surgery. In a ten-year study of deep sclerectomy with collagen implant, approximately 60% of patients required laser goniopuncture postoperatively to maintain function.

The newest approaches to glaucoma surgery include canaloplasty (iScience Interventional, Menlo Park, CA), in which Schlemm's canal is circumferentially catheterized and dilated with Healon GV (sodium hyaluronate, Advanced Medical Optics, Santa Ana, CA) using an iTrack 250 Canaloplasty Microcatheter™ 200 microns in diameter with a diode light at its tip, allowing the iTrack™ to be viewed through the sclera providing physician guidance during the procedure [Figure 2]. Once the canal has undergone 360° catheterization, a 10-0 Prolene suture (Ethicon Inc, Somerville, NJ) is attached to the microcatheter and pulled around as the iTrack™ is withdrawn and viscodilation occurs. This suture, when tensioned, stretches the TM internally and in initial studies, lowers IOP. Interim study results demonstrate significant reduction in IOP with mean IOP of 16.3 mmHg two years after canaloplasty and 13.4 mmHg after combined canaloplasty and cataract surgery. Medication use decreased in both study groups and serious complications such as hypotony were infrequent.

The Trabectome (NeoMedix Inc, Tustin CA) provides direct access to the distal outflow channels by removing a strip of meshwork and inner wall of Schlemm's canal allowing direct communication between the anterior chamber and collector channels (Figure 3). This ab interno trabeculectomy was FDA approved in 2004. The Trabectome tip includes a foot-pedal controlled bi-polar cautery unit that ablates tissue with simultaneous aspiration of debris via a 25 gauge tube. The hand piece includes an 18 gauge infusion sleeve allowing gravity

controlled infusion of balanced salt during surgery. Transient intra-operative hyphema due to blood reflux into Schlemm's canal usually resolves within the first week. Initial results are promising, with IOP reduction in the 40% range at 36 months and limited data showing prolonged reduction (IOP reduction of 32%) at 60 months. Immediate post-operative elevation of IOP may occur infrequently (5.8%) but there is no bleb formation or risk for flat anterior chamber and peri-limbal conjunctiva is preserved if further surgical intervention becomes necessary.

Another innovation is the Glaukos iStent (Glaukos Corp., Laguna Hills, CA). This trabecular micro-bypass stent is an L-shaped titanium tube that is implanted ab interno into Schlemm's canal with an inserter via a small opening through TM. The iStent bypasses the trabecular meshwork and restores aqueous flow from the anterior chamber into Schlemm's canal [Figure 4]. Again, no bleb is formed and the placement of the iStent preserves all future options for glaucoma filtering surgery. A small case series with the latest version of this device has demonstrated post-operative intraocular pressures of 14 mmHg-15 mmHg at 12 months. In tissue-culture autopsy eye studies, multiple implants were demonstrated to further reduce IOP than one implant. Interim analysis of a study combining iStent implantation and cataract surgery showed a mean decrease in IOP of 18.3%.

The SOLX Gold Shunt (Solx Inc, Waltham, MA) is an implantable drainage device designed to reduce elevated intraocular pressure associated with glaucoma. The device is fabricated from biocompatible, 99.95% pure gold and provides a pathway for the flow of aqueous humor from the anterior chamber of the eye to the suprachoroidal space, utilizing a natural drainage pathway within the eye [Figure 5]. Ongoing clinical studies have demonstrated the safety and efficacy of the Gold Shunt. A pilot study has demonstrated a mean 36.2% or 9 mmHg decrease in IOP (27.6 mmHg to 18.2 mmHg) using the first generation of this device. European data from open label studies of the second generation Gold Shunt demonstrated pressure reductions of 49% maintained to one year with fewer adjunctive glaucoma medications. Serious complications following implantation of the Gold Shunt are rare.

Several types of aqueous shunts (glaucoma drainage devices) are now employed, usually in complicated cases when other surgical approaches have failed. A glaucoma drainage device (GDD) consists of an equatorial endplate of varying surface area and design that is inserted via either a limbal or fornix based conjunctival flap under Tenon's capsule. The end-plate is attached to a drainage tube inserted into the anterior chamber or the posterior chamber after vitrectomy via the pars plana. GDDs direct fluid into an external equatorial filtering bleb developed around the explant plate. Initially after installation, non-valved shunts (Baerveldt, Molteno) offer little or no resistance to outflow, but may be transiently constricted with a surrounding ligature with a variety of techniques. Two devices (Ahmed, Krupin) include valves or flow restrictors that decrease the rate of immediate hypotony without the need



Figure 2. Intraoperative photo of iTrack 250 Canaloplasty Microcatheter™ (Courtesy of iScience Interventional, Menlo Park, CA)

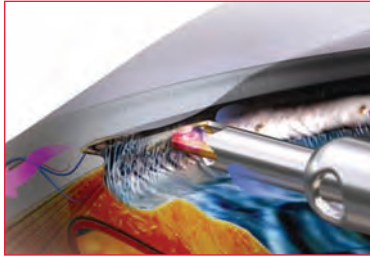


Figure 3. Schematic representation of Trabectome procedure. (Courtesy of Neomedix Inc, Tustin, CA)



Figure 4. Scanning electron microscopy of iStent trabecular micro bypass stent. (Courtesy of Glaukos Corp, Laguna Hills, CA)

thinner walled capsule with maximized surface area to enhance filtration. Drainage implants, or tube shunts, have traditionally been reserved for patients who have uncontrolled IOP and a history of failed filtration procedures, scleral buckling surgery, extensive conjunctival scarring or exaggerated inflammatory response (neovascular or uveitic glaucoma). Interestingly, implants are being done more commonly and some glaucoma surgeons are using them as their primary filtration surgical modality.

Cyclodestructive procedures are reserved for refractory glaucoma in eyes with failed filtering or drainage implant procedures and poor visual prognosis. The ciliary epithelium is damaged using transscleral laser or cryotherapy, which decreases aqueous production. Cyclocryotherapy is a freezing technique that creates significant ocular tissue damage and is non-selective for the ciliary epithelium. Pain, inflammation, hypotony and phthisis are common side effects. Cyclophotocoagulation can be performed externally (transcleral) or internally (endoscopic) with laser energy that is selective for the melanin in the ciliary epithelium to result in relatively localized damage. The transcleral approach employs an Nd:YAG, diode or krypton laser and generally results in less inflammation and pain than cyclocryotherapy. Endoscopic cyclophotocoagulation (ECP) uses an 810 nm pulsed continuous-wave diode laser combined with a high-resolution fiber optic camera to selectively ablate the anterior ciliary body processes (Endo Optiks, Little Silver, NJ). An advantage of this procedure is the ability to directly visualize



Figure 5. Schematic representation of SOLX Gold Shunt. (Courtesy of SOLX Inc, Waltham, MA)

for a surrounding ligature. A recent randomized trial (Tube vs. Trabeculectomy Study) with one-year follow-up found IOP results equivalent comparing a GDD to trabeculectomy with MMC. Drainage implants can reduce IOP 50% below pre-operative levels. However, they are also associated with complications including hypotony, corneal decompensation, encapsulation of end-plate, erosion of tube or plate, suprachoroidal hemorrhage and diplopia. A newer device, the Oculieve (Aqueous Biomedical, Colorado Springs, CO) may reduce these complications by creating a smaller volume,

development of new imaging techniques and materials. The ultimate goal of surgical intervention is to achieve long term IOP control with lower risk for surgical complication.

Glaucoma surgery will continue to evolve with the

development of new imaging techniques and materials. The ultimate goal of surgical intervention is to achieve long term IOP control with lower risk for surgical complication.

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9 | Adherence in Glaucoma Therapy

Steven R. Hahn, MD

Patients do not benefit from medicines they do not take and most clinicians are aware that patients commonly fail to take all the medication that they are prescribed. Yet nonadherence does not receive attention proportionate to its recognized importance in clinical practice. Although some physicians may need to be reminded about the magnitude of the problem, it is not a fundamental ignorance of nonadherence that explains the lack of attention it receives. One answer may be that clinicians intuitively know what research on adherence has demonstrated: Nonadherence is difficult to detect, its causes may be hard to identify, and the factors that determine adherence often seem to be beyond the clinician's control or scope of clinical expertise. These beliefs may create a sense of powerlessness that is ultimately rationalized by the feeling that nonadherence is a

revelation of the imperfection of human nature and might as well be accepted. The goal of this chapter and the next one addressing doctor patient communication is to reverse this pessimism and empower clinicians by providing necessary information on the prevalence and causes of nonadherence and, in the next chapter, communication strategies to aid in detecting nonadherence and its causes, and in enhancing motivation and lowering barriers to adhere.

Patient compliance was the term originally used to describe the extent to which patients take medication and follow lifestyle and behavioral recommendations prescribed by their clinicians. The term "adherence" has largely supplanted "compliance" because the latter carries the connotation of a paternalistic clinician-directed relationship in which patients "comply" with the directives of their doctor. By contrast, adherence connotes a patient's willingness to "stick to" a treatment that they have agreed upon with their clinician. A consensus panel convened by the World Health Organization chose to define adherence as "the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider." Persistence is one aspect of adherence and refers to the extent to which patients sustain use of medication and lifestyle changes and behavioral treatments over time.

The first, and probably most important problem presented by noncompliance is the difficulty of detecting it. Numerous studies have demonstrated that patients consistently under report and, as discussed in the next chapter, actively conceal nonadherence from their clinicians. A meta analysis of 86 studies revealed that patients consistently overestimated adherence to treatment compared to non-self-report methods of measuring medication taking behavior. Concordance between face to face interview-based self-report was particularly low with electronic event monitors and somewhat better with adherence questionnaires and diaries, pill counts, insurance claims analyses, and plasma drug concentrations. Clinicians' assessments of adherence are inaccurate and tend to over-estimate adherence; in one recent study of 181 glaucoma patients, physicians thought that 71% of nonadherent patients were adherent and 28% of adherent patients were nonadherent. One reason for under detection in addition to relying on patients' self-report may be reliance on measurement of rapidly responsive physiological parameters such as intraocular pressure at the time of a doctor visit, because patients are often more adherent to medication just before their visits to the doctor. This so-called "white coat adherence" has been observed in several therapeutic areas including glaucoma. Although self-report of nonadherence may be an insensitive measure of the problem, it is reasonably specific. A meta analysis of four studies comparing patient self-report to pill count, showed that asking patients if they had missed any doses of any medication detected 55% of patients defined as nonadherent by pill count (sensitivity), and had a specificity of 87%. Nonadherence to treatment is common across therapeutic areas. In a quantitative survey of 569 studies published between 1966 and 1998 adherence ranged from 4.6% to 100% with a median of 76% and an overall average of 75.2%. Rates of adherence varied significantly with the methods used to measure them from a low of 66.6% for collateral report and 69% for MEMS caps to a high of 85% for pill count. Rates of adherence to behavioral interventions such as diet and exercise are often as low as 10%.

Although there is no gold standard for adherence measurement, the use of surreptitious electronic devices (MEMS recorders) that

record the opening of a pill bottle, or use of a medication dispenser is one of the most reliable methods. In studies of adherence to glaucoma medications using MEMS devices almost half of patients (41%) miss 10% of three times daily pilocarpine doses, i.e., one dose in every two days. In another study using the same technology, more than a quarter of patients (27.3%) missed more than a quarter of timolol doses when used either alone or in combination with pilocarpine or another medication, and a small but significant number of patients (8.2% and 15.2%) missed half or more of their medications. In a recent study, 44% patients using a travoprost electronic dosing aid that recorded and reported medication use took fewer than 75% of doses. Medications that are taken more than once per day are also vulnerable to problems with the timing of doses. Morning medications are taken more reliably than doses later in the day and noon doses are the most frequently omitted. Studies using MEMS recorders are usually of short duration, and typically over sample more persistent patients and under sample those new to treatment. In theory, analysis of pharmacy claims data presents an opportunity to study patients who are new to treatment and follow adherence behaviors over a longer period of time. An early study using this approach suggested that one quarter of 2,440 patients who filled an initial prescription for glaucoma medication never filled a second one and overall, patients were without medication for nearly a third (30%) of the 12 month period that was studied. Another study of 3,623 patients with diagnosed glaucoma and 1,677 glaucoma suspects, all apparently newly treated, revealed that nearly half had discontinued all glaucoma medication by the end of one year.

The Glaucoma Adherence and Persistence Study (GAPS), based upon retrospective analysis of the pharmacy and medical claims data of 13,956 subjects patients on glaucoma medication revealed significant problems with nonadherence that are consistent with previous studies. The principal measure of adherence used in GAPS was the medication possession ratio or MPR, calculated by dividing the days of supply of medication dispensed by the number of days between prescription fulfillments. The MPR is therefore a ratio expressing the proportion of days for which a patient possesses enough medication to use drops as directed. Although 89% of subjects claimed to take their glaucoma medication "every day," the average medication possession ratio (MPR) observed in GAPS was 0.64 (median 0.57), meaning that the average subject only had enough medication to take 64% of prescribed doses. The most poorly adherent 25% of subjects possessed enough medication to take no more than 36% of their prescribed doses, by contrast the most adherent 25% possessed enough medication to take 88% of their doses. Over half (55%) of the 10,260 subjects followed for at least one year stopped and restarted medications within that 12-month period. Only 10% of subjects filled prescriptions continuously for 12 months.

Our understanding of the causes of nonadherence has evolved from the original "Health Beliefs Model" which proposes that adherence to treatment is the result of a balance by the patient's perception of their vulnerability to and the threat of the illness, the benefit of the treatment, the cost and burden of the treatment, and social and instrumental support for adherence. This model has evolved to focus on specific elements within these domains. For example, the "Information, Motivation, and Behavioral Skills" (IMB) model asserts that these are the three key independent determinants of adherence. This model makes the observation that patients can be motivated to adhere without being knowledgeable about the illness and vice versa,

but they must have the specific information that supports critical behavioral skills, such as those required for administration of drops, or for creating and integrating behavioral triggers to prompt medication taking into the daily routine. The closely related "Therapeutic Decision Model" calls attention to the fact that patients' decisions about adherence are dynamic and incorporate ongoing experience of side effects and efficacy with their providers' recommendations and other sources of information. Most patients engage in an active testing process that usually remains obscure to clinicians because they do not actively explore it with their patients. Finally, emerging research has demonstrated the predictive power of the two-factor, "Beliefs in Medication" model which proposes that adherence is the net effect of belief that medication is necessary balanced by concerns about taking medication. These two factors are independent of one another, thus an ambivalent individual may believe that medication is necessary yet be equally or more concerned about the consequences of taking medication.

Factors influencing adherence have generally been classified into four categories: patient characteristics, provider characteristics, characteristics of the medical regimen, and situational/logistical factors including cost. Tsai and colleagues identified 71 specific barriers that patients reported interfered with using glaucoma medication. Patients' socio-demographic characteristics have been inconsistently associated: a review of early research in adherence to glaucoma medication found that age, and education were not associated with non-adherence, that ethnicity and male gender probably were, but weakly and inconsistently. With regards to characteristics of the regimen, increase frequency of dosing but not number of medications, total number of medicines for all conditions, and frequency of side effects have been related to nonadherence. Several studies have documented better adherence for prostaglandins compared to other classes of medication. Cost of medication and the need to integrate medication taking with the daily routine have been associated with adherence.

The result of GAPS identified eight independent factors associated with nonadherence, five of which are amenable to clinical intervention: (1) hearing all of what you know about glaucoma from your doctor (compared with some or nothing), i.e., "doctor-dependent learners"; (2) not believing that reduced vision is a risk of not taking medication as recommended, i.e., the "unconcerned"; (3) having a problem paying for medications; (4) difficulty while traveling or away from home; and (5) not receiving a phone call visit reminder. If perceived need for medication is adhering to treatment, then a robust understanding of the consequences of glaucoma in the future is the foundation of critical "motivating concern." GAPS revealed that, despite almost three years of therapy on average, 14% of patients were not concerned that nonadherence could lead to vision loss. They shared in common with the third of patients who were "doctor-dependent learners" who learned everything they know about glaucoma from their doctors, the experience of not having heard from their doctor what to expect in the future from glaucoma. Doctor-dependent learners reported other deficits in their understanding of glaucoma and their communication with the physician; they were the least confident in their knowledge about glaucoma, reported that doctors didn't ask them if they had questions or understood, and got fewer satisfactory answers to the questions they did ask. Patients who do not have a robust understanding of what glaucoma might do in the future are less likely to adhere to treatment. Patients who passively depend upon their providers and don't actively engage in developing their understanding of the disease are less likely to be successful in

sustaining their motivation and in overcoming barriers to adherence. The results of GAPS also point towards cost, taking medication while traveling and away from home, and the physician's practice communication style as modifiable factors influencing adherence.

Nonadherence to topical glaucoma medication is prevalent and difficult to detect because nonadherence is a socially undesirable behavior which patients are reluctant to reveal. Current understanding of adherence behavior identifies the need for patients to understand the progression of the disease over time in a way that supports concern about future consequences. They also need to have the behavioral skills necessary to remember and administer medication. Patients who are actively engaged in learning about glaucoma and interested in participating in decision making are most likely to overcome barriers to adherence. Providers can screen for active engagement in self-care and for the presence of a motivating concern about consequences by asking patients to describe their understanding and concerns about what glaucoma might do in the future. The epidemiology of barriers to adherence support the value of screening for specific barriers to adherence such as cost of medication, taking medications while traveling and away from home, and the mechanics of drop administration. Communication strategies for addressing these factors are addressed in the chapter on communication.

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10 | Communication in the Management of Glaucoma

Steven R. Hahn, MD

A patient's daily decision to use glaucoma medication is the result of a balance between their understanding of the potential risks of glaucoma, their belief in the benefit of medication and the burden of taking their drops. For most patients, the risk of untreated glaucoma is an idea about potential future loss of vision. On the other hand, the burden of treatment is not an idea; it is a tangible daily experience. Although not as burdensome as treatment for many other conditions, glaucoma is vulnerable to all the barriers to adherence associated with any chronic medication and some unique ones as well. In addition to inconvenience, cost, and integration into daily lifestyle, topical glaucoma medication is technically more complex to administer than a pill and often associated with unique nuisance side effects.

If adherence is the net balance of "perceived need for medicine," with the burdens and "concerns about taking medicine," and clinicians are the most important and sometimes only source of understanding about glaucoma, then adherence is very much the story of the struggle between the effect of patients' episodic communication with their clinicians and the daily experience of taking drops. In short, clinician-patient communication is the foundation of adherence, and adherence is the key factor in treatment outcome, for patients do not benefit from medicines that they do not take.

There are significant barriers to the detection of nonadherence in patients prescribed chronic medications. Research has demonstrated that physicians have no better than a 50-50 chance of detecting nonadherence in their patients. In glaucoma in particular, a recent study demonstrated that physician thought that 71% of nonadherent patients were adherent and misclassified 28% of adherent patients as nonadherent. Three studies of occult nonadherence from studies of chronic diseases are illustrative:

Patients with "treatment resistant hypertension" who had told their physicians that they were taking their medications consistently were told to continue their current treatment regimen using a pillbox that they knew would record when they took their pills. Subjected to this scrutiny, one-third of the patients were instantly "cured;" however, several had syncopal episodes when they complied with regimens that had previously been intensified in the mistaken belief that they been adherent. Another 20% of the subjects remained uncontrolled, but the recording pill box demonstrated that the cause was nonadherence. In another study, in this case using surreptitious micro recording devices, Cramer et al demonstrated that adherence to antihypertensive treatment was 88-86% during the week before and after a visit to the doctor, but was only 67% six weeks earlier or later. Finally, home glucose diaries were compared to memory chip values in 19 Type I diabetics who were surreptitiously given the first generation of glucometers with a recording memory. Over all, half the patients made up half the values, and physicians had a 50-50 chance of predicting which patients and values were fabricated.

Why should patients conceal nonadherence from their clinicians? Patients realize that providing misinformation may lead to poor decisions about treatment, but their behavior is shaped by a more powerful force: Nonadherence is a "socially undesirable" behavior and patients want to be seen as "good patients." This desire is often stronger than their concern that concealing nonadherence might lead to bad decisions about treatment. This tendency is exacerbated by the fact that patients expect their clinicians to be judgmental. Unless the clinician does something to alter it, the default perception of the patient is that the clinician will think they are a bad patient and be unsympathetic to any reason they have for not taking medication as directed. Understanding these key features of the psychology of patient self-report of nonadherence is the foundation for a four-step, semi-structured dialog that reduces barriers to admitting to nonadherence by reversing the judgmental environment and redefining the "good patient" as one who collaborates in solving treatment problems.

The four steps of the adherence detection interview are (table 1):

1. Begin with a directive open-ended question: "Tell me how you've been taking your medications." The patient's response will reveal their level of understanding of their regimen. Follow up with a question about how they organize their medication and remember to take them. It is useful to have the patient describe the way they use all of their medications (both topical and systemic) even if the clinician asking is focused on the use of only some of them.

2. Change the patient's expectation that you will be judgmental: Tell the patient that you know that noncompliance is "universal," everyone has difficulty adhering to a medication regime, and it is "normal" or understandable if a dose is missed because of problems such as cost, side effects, inconvenience, etc.

3. Explain how information about adherence will affect decisions about medication: For example, "Your pressure is higher

than it should be. Before we change the prescription, let's make sure that you've been able to use the medications you're already on. Taking too much medicine or changing to a second-choice medication would not be the best thing if the real problem has been with taking the medication you've already been prescribed." This intervention is important because it changes the definition of a "good patient" from the unrealistic expectation that the patient will always be adherent, to an understanding that a "good patient" is one who discusses and solves problems with adherence with the clinician.

4. Finally, ask about "forgetting" or "missing" medications:

The critical feature of the fourth step in the sequence is that it comes last, after the stage has been set. If the patient claims to be adherent before steps one through three, the task of getting the real story becomes doubly difficult because the patient will have to admit to having not told the whole truth on top of now having to acknowledge their nonadherence.

When problems with adherence are detected, the clinician needs to assess two things: the patient's motivation to take the medicine and the presence of specific barriers to adherence. Even a patient who experiences no burden or barrier to taking a medication will not take it without believing there is a good reason to do so. Therefore the strategy is to determine that the patient is concerned about the consequences of glaucoma and believes that taking it will be beneficial. The tactic for this assessment is to use "Open-Ended Questions" about concerns and perceived benefit in an "Ask-Tell-Ask" sequence.

Consider the Following Dialog:

Optometrist: "Are you concerned about the consequences of glaucoma?"

Patient: "Yes."

Compared With:

Optometrist: "Tell me what you understand about glaucoma, and what your concerns are?"

Patient: "Well, I'm not really sure because I haven't noticed any difference in my vision except for what the new glasses corrected. I mean my vision is fine when I wear my glasses. I thought glaucoma was where you had real problems seeing. I was told that my pressure is too high by the last doctor who saw me, the one who put me on the drops, but my pressure was high before and I was told there was no need for treatment. So I don't really know what to expect, or whether I should worry or not."

The first question is "closed-ended"; one that calls for a yes or no answer. The second is an "open-ended question"; one that cannot be answered yes or no, but rather calls for a broader response. This open-ended question is still focused. It is a "directed" open-ended question that points the patient's response to a particular domain—concerns about and understanding of glaucoma—but does not constrain the way the patient answers.

The directed open-ended question, "Tell me what you understand about glaucoma, and what your concerns are" is the first "ask" in a three step "ask-tell-ask" pattern that forms the basic building block of all patient education interventions. The first ask of the sequence will tell you three things: What the patient already knows; what the patient doesn't know; and the patient's misconceptions and mistaken beliefs.

In the sample dialog above, the clinician learns that the patient:

- Knows his "pressure is too high" and that the last doctor recom-

mended medication.

- Doesn't understand why medication was started, specifically why his high intraocular pressure wasn't a reason for starting medication before but is now.

- Has the mistaken belief that he does not have glaucoma unless he is experiencing noticeable vision loss.

It is far better to learn what the patient already knows than it is to launch into a set patient-education speech for at least two reasons. First, the clinician can avoid spending unnecessary time on information the patient already has. Second, asking first allows the clinician to overtly acknowledge the patient's correct understanding thereby reinforcing his self-confidence, sense of self-efficacy, and praising him for his ability to collaborate in self-care and decision making.

In our sample dialog, the clinician can tell the patient:

"You're right, your pressure is too high, and that does produce the problem of glaucoma if it is not corrected. It is time for medication in your case..."

The patient's understanding of glaucoma and medication is like a partially assembled jigsaw puzzle. Once the clinician understands which pieces have been connected and which are not yet aligned, it will become clear which piece of the puzzle needs to be put in place next to allow the rest to fall into place. A set speech on glaucoma may include the critical information, but if it is presented along with too much information or at the wrong time the patient will not be able to integrate it.

In our sample dialog, the clinician can tell the patient:

"...But high pressure in the fluid in your eye is not the whole story of glaucoma and when you need treatment. The pressure causes damage to the nerve that goes from the eye to the brain, and we detected the beginning of damage in that nerve at the last visit by testing your visual fields, the machine with the flashing lights. That's why we knew that you need treatment." Perhaps the most important benefit of asking before telling is the opportunity to identify the patient's misconceptions and mistaken beliefs. Erroneous beliefs dramatically interfere with patients' motivation to adhere and self-care behaviors. An undiscovered error in understanding can render all of the correct information a clinician might provide useless. What is truly striking is how prevalent and unpredictable patients' mistaken beliefs can be across all chronic diseases. The only way to discover the patient's mistaken ideas is to ask.

In our sample dialog, the clinician can tell the patient:

"...A lot of people believe that they don't have glaucoma unless they notice a problem with their vision in everyday life. We can detect the problem of glaucoma before you can yourself, and that's a good thing because it gives us a chance to prevent more serious damage."

If the first ask reveals the patient's initial knowledge, missing information, and misconceptions, the "second" ask reveals what has happened to those dimensions of the patient's understanding as a result of the "tell", and also takes the dialog on to the next step of explanation or instruction. The second ask should take the general form, "What questions or concerns do you have now that you have heard what I just told you." In our sample dialog, the patient's response to this second question was: "So you mean I've already got damage to my eye? How bad is it? You said 'prevent more serious damage,' the medicine will do that? And what was that about the visual field test?"

The second ask continues the dialog, and lets the clinician know

Learned from the first "ASK"

1. What the patient already knows that is correct and important.
2. What the patient doesn't know that they should.
3. The patient's misconceptions and mistaken beliefs.

Focus of the "TELL"

Reinforce what the patient understands correctly, without wasting time.
 Prioritize and present the next most important pieces of information.
 Correct misconceptions and mistakes.

Learned from the second "ASK"

Assess improvement in confidence, self-efficacy and commitment.
 Assess comprehension and impact of new information.
 Assess comprehension and impact of corrected understanding and beliefs.

Table 1

which parts of the "tell" got through and which didn't. Our patient's response to the second ask makes it clear that the patient needs to learn a little more about the stage and severity of his problem, is ready to hear a reassuring link between medication and preventing vision loss, and didn't quite get the role of visual fields in managing glaucoma.

Unfortunately, current clinical practice rarely employs these patient-centered communication strategies. A recent study of 50 patient encounters with 23 ophthalmologists demonstrated that these four steps, or their equivalent, are rarely employed in current clinical practice. Physicians were observed to ask an average of 5.6 questions during the average 5.8 minutes they spent talking to their patients. They rarely (6% of questions) asked patient-centered open-ended questions that are likely to lead to substantial discussion of patients' perceived need for medication or concerns about taking it.

Adherence is a result of the balance between a patient's concern about the consequences of glaucoma, their belief in the benefit of treatment, and the burden of taking medication. Communication between clinician and patient is the foundation of patients' understanding. Communication about adherence to medication is challenging because patients would rather conceal nonadherence than be perceived as bad patients. This barrier can be lowered by using a four-step semi-structured dialog that addresses the psychology of acknowledging socially undesirable behavior. Patient motivation and specific barriers can be discovered and addressed using open-ended questions in "ask-tell-ask" interviewing sequences that focus on perceived need for medication, concerns about taking and integrating medication use in daily life.

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Secondary glaucomas are defined as the presence of elevated intraocular pressure (IOP) and/or glaucomatous damage as the result of a specific causative etiology. Secondary glaucomas are often identified using a targeted history which would include specific questions regarding past injury or surgery as well as the current or past use of corticosteroids. A deliberate anterior segment examination including gonioscopy may reveal evidence of one or more causes of secondary glaucoma. While there are numerous forms of secondary glaucomas the following discussion focuses on four of the more common types.

PSEUDOEXFOLIATION AND PSEUDOEXFOLIATIVE GLAUCOMA

Pseudoexfoliation is seen as a gray white material that accumulates within the eye. This fibrillar substance has elastic properties and may be found in various structures throughout the body including skin, heart, lung, kidney, liver and cerebral meninges. While definitive support for systemic associations is lacking, it may be forthcoming as more is understood about this condition. Deposition of this material occurs predominantly on the structures of the anterior segment with the earliest sign being a dull gray diminished luster of the anterior lens capsule. This thin grayish white sheet may become patchy and discontinuous resulting in superficial gray flakes or scrolls of tissue. Movement of the pupil may cause the material to be pushed centrally and peripherally resulting what has been described as a bull's eye pattern. Contact between the iris and the lens may cause pigment to be liberated from the posterior surface of the iris. Subtle, peripupillary transillumination defects may also be evident. Each of these findings may be more evident when the pupil is dilated. Pigment may be deposited on the corneal endothelium and in the anterior chamber angle; dandruff-like flakes may be visible on the ciliary processes, zonular fibers, lens, iris, and in the angle. IOP elevation is associated with the deposition of pseudoexfoliative material and pigment within the trabecular meshwork, and structural and functional alterations there, interfering with aqueous outflow.

Pseudoexfoliation is found worldwide with varying prevalence rates reported. It has been reported to be the most common identifiable cause of open-angle glaucoma. This could be particularly useful to identify in patients with asymmetric glaucoma and when widely variable intraocular pressure measurements are found.

The presence of pseudoexfoliative material does not constitute a diagnosis of glaucoma. Conversion from pseudoexfoliation to the development of glaucomatous damage (pseudoexfoliative glaucoma) is variable depending on the population and length of follow up reported, with conversion increasing with age to a level that may reach 40%. It is often unilateral or asymmetric especially early in the presentation. Progression from unilateral to bilateral presentation is also variable, increases with age and is reported to range from 15-40%. Grodum et al showed that patients with pseudoexfoliation and ocular hypertension were more likely to develop glaucomatous damage than age and intraocular pressure matched patients without pseudoexfoliation (55.1% vs. 27.6% in over eight years of follow up). Pseudoexfoliative glaucoma may be a more aggressive form of glaucoma than primary open-angle glaucoma. Intraocular pressure may be more variable in eyes with pseudoexfoliation with wide swings and abrupt

changes in level of control of intraocular pressure. Depending on the clinical circumstances, including the extent of damage, this may prompt the clinician to follow the patient at shorter intervals and attempt more aggressive intraocular pressure control. Therapy is similar to primary open angle glaucoma, with excellent response to laser trabeculoplasty. Recently, three common sequence variants in the lysyl oxidase-like 1 (LOXL1) gene were found to be associated with both pseudoexfoliation (PEX) and pseudoexfoliation glaucoma in individuals from Iceland. These genetic variants in LOXL1 demonstrate a risk to developing PEX.

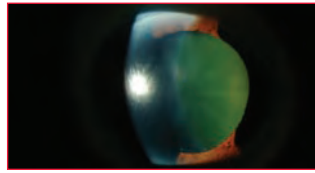


Figure 1. Slit-lamp photo reveals subtle gray concentric curvilinear deposition lines on the anterior lens capsule with an intermediate clear zone.

PIGMENT DISPERSION AND PIGMENTARY GLAUCOMA

Pigment dispersion results from pigment liberated from the posterior surface of the peripheral iris due to iridozonular contact. Clinical manifestations of pigment dispersion include pigment accumulation on the corneal endothelium (often in a vertical arrangement, Kruckenberg spindle), in the anterior chamber angle and on the zonular fibers, particularly at the interface of zonular fibers and lens capsule (Scheie Stripe). There is often iris transillumination defects which are linear or slit-like in the equatorial or peripheral iris. The anterior chamber is deep and there may be an observable posterior bowing of the iris. Occasionally excessive pigment may be liberated from a secondary cause such as iris chafing on an intraocular lens (secondary pigment dispersion).

The prevalence of pigment dispersion and incidence of related glaucoma is not well known. The mechanism of elevated intraocular pressure is related to impaired aqueous outflow through the trabecular meshwork. There may be a mechanical obstruction due to pigment granules in the trabecular meshwork. There are also increased phagocytic and metabolic demands on the endothelial cells that lead to degenerative changes in the trabecular meshwork anatomy. Pigment dispersion refers to signs being present without the elevation of IOP. When elevated IOP is discovered, the patient is labeled as having pigmentary glaucoma. Management of IOP elevation is similar to other open angle glaucomas with prostaglandins often the first class of drugs considered.

CORTICOSTEROID INDUCED GLAUCOMA

Exposure to corticosteroids may produce an elevated intraocular pressure in susceptible individuals. The likelihood, extent and rapidity of onset is related to the agent used, route of administration, and individual susceptibility. A steroid response is more likely in patients with a personal or family history of open angle glaucoma. While topical, intraocular and periocular administration are most likely to produce an increase in intraocular pressure, systemically administered, including inhaled steroids as well as topical applications remote to the eye may contribute to



Figure 2. Scheie stripe.

elevated pressure. With the expanding role of intravitreal steroids (injections and implantable devices) the clinician should be aware of the possibility of secondary elevation of intraocular pressure which may be severe or difficult to control. Appropriate follow up for an extended post injection period is indicated especially in those with a family history of glaucoma or who have demonstrated susceptibility to corticosteroids in the past.

The mechanism of the increased intraocular pressure is believed to be increased resistance in the conventional outflow pathway. This is very often reversible except in cases of long term elevated pressure. It is important to take a thorough history when IOP elevation is discovered to elicit whether steroids agents are being used and may be the culprit. Another clinical circumstance that may present is the patient who appears to have normal tension glaucoma that in fact has suffered prior damage during prolonged courses of corticosteroids in the past. Alert those patients requiring treatment with corticosteroids to have their IOP measured periodically while under treatment. Clinicians may wish to obtain baseline stereodisc photographs of patients with the potential for steroid induced elevations of intraocular pressure. Treatment of the elevated pressure is discontinuation or substitution of the causative agent if possible and management of the intraocular pressure as appropriate for the clinical circumstances.

GLAUCOMA ASSOCIATED WITH TRAUMA

Several signs and the past history may suggest prior ocular trauma. Iris sphincter tears, traumatic mydriasis, cataract, iridodialysis, cyclo-dialysis and recession of the anterior chamber angle are also sequelae to blunt trauma of the globe. Recession of the anterior chamber angle appears as a deep anterior chamber evident on gonioscopy as a broadening of the ciliary body band (CBB) and a posterior or deeper insertion of the iris. The extent of angle recession may serve as a marker for the degree of injury. The mechanism of elevated intraocular pressure is reduced aqueous outflow related to damage to the trabecular meshwork; not the actual recession per se. The incidence of glaucoma is variable but is often reported around 10% of those with angle recession.

Glaucoma associated with prior trauma follows similar management strategies as primary open angle glaucoma except for the use of laser trabeculoplasty which should be avoided given a lower success rate. There is also a possibility for an acute IOP elevation associated with laser trabeculoplasty when performed on scarred and anatomically abnormal trabecular meshwork.

Secondary glaucomas are relatively common and need to be recognized as being present since the management and prognosis may vary depending upon the form present.

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12 | Primary Angle Closure Glaucoma

David S. Friedman, MD, MPH, PhD

Primary Angle Closure Glaucoma (PACG) is a leading cause of blindness worldwide. In China it is estimated that nearly one in six individuals over the age of 50 has an angle appearance that puts him/her at risk of PACG and acute angle closure attacks. Asian populations are aging so the number of people with PACG will increase dramatically in the coming decades. While it is often said that Chinese populations (and others in East Asia) have ten times of the risk of PACG as European derived individuals, the truth is that in carefully conducted research studies the number is closer to four times as much, and nearly one in 200 European derived individuals over the age of 40 has PACG. The proportion with PACG increases with age, so many older European derived individuals have PACG and these cases are frequently missed or misdiagnosed. Furthermore, it is essential that adequate evaluation is given to higher risk populations (older persons, Asians, and in particular, older women).

In order to focus this chapter, I will first review the terminology used when referring to patients with PACG and then will discuss the epidemiology of PACG. The remainder of this chapter will cover diagnosis and treatment strategies for PACG.

To allow for more uniform reporting and to improve how we think about the mechanisms of angle closure a new terminology was proposed and subsequently modified during a consensus panel meeting involving over 100 glaucoma specialists from around the world. There are currently four categories for describing persons with angle closure, three of which require specific gonioscopic findings. Each of these requires that the pigmented trabecular meshwork is blocked by iris (what is termed "iridotrabecular contact or ITC") in at least one quadrant. There is no firm agreement on how many quadrants must have ITC for "angle closure" to be present, but current consensus appears to be that at least 180 degrees is required. This lack of consensus is largely due to the lack of prospective information on what happens to untreated individuals with ITC. The amount of ITC is determined in a dark room using a one mm beam on a bright setting while performing gonioscopy. Greater amounts of illumination (a long wide beam, for example), will allow light to enter the pupil which can artificially open the angle and cause cases of angle closure to be missed.

1. Primary Angle Closure Suspect (PACS): Some eyes have no other findings than ITC on gonioscopy. There is no "disease" present, and no evidence of harm to the patient. The clinician is concerned by the appearance, but the intraocular pressure (IOP) and the optic nerve are both normal, and there are no peripheral anterior synechiae (PAS). How much angle closure must be present to apply this categorization remains controversial, but I typically

use 180 degrees or more. Gonioscopy is performed using the small bright beam having the patient look straight ahead and only modestly tilting the lens if the view is difficult. This is a somewhat subjective evaluation, but there are no better approaches currently available. There is ongoing debate whether these persons require iridotomy to avoid the development of PACG or acute attacks.

2. Primary Angle Closure (PAC): This category includes people with ITC for 180 degrees or more as described above for PACS who have additional findings on examination. These people have some evidence that the angle appearance is causing harm to the eye. More specifically, they have either PAS or elevated IOP, but they do not have optic nerve damage and visual field loss. This condition is considered pathologic (although there are almost no long-term data on people with these findings), and most clinicians recommend laser iridotomy for these people.

3. Primary Angle Closure Glaucoma (PACG): This category requires the presence of ITC for 180 degrees or more as described above for PACS and PAC along with glaucomatous optic neuropathy and visual field loss. This definition of "glaucoma" is the same as one would expect for open-angle glaucoma.

Finally, there is a category called a primary acute angle closure (AAC) attack which presents with classic signs and symptoms. Patients have very elevated IOP, the angle is closed, the conjunctiva is red, the cornea frequently is cloudy, and the patient has eye pain and may have nausea and vomiting.

Others have used the term "Mixed Mechanism" glaucoma to describe people who develop glaucoma in spite of an open angle after iridotomy. While some of these persons might have more than one mechanism causing optic nerve damage, the issue of how to describe them is essentially semantic since treatment remains similar once an iridotomy has been performed. I feel these patients have PACG.

PACG occurs in about 0.5% of whites and blacks over the age of 40, and about 1.5% of Chinese and sub-continental Indian individuals in this age group, but is much more common in older populations. Recent studies indicate that even in high prevalence countries such as China, open angle glaucoma is more common than PACG. However, even though PACG accounts for about a third of all glaucoma cases in China, most of the 5.2 million people blind from glaucoma have PACG indicating that glaucoma is frequently more severe when associated with angle closure. Similar findings were reported for Asian Indians where 41% of those with PACG were blind in one or both eyes from PACG.

PACG is associated with a relatively anterior lens position and a proportionally thicker lens, both of which result in a relatively shallow anterior chamber depth, one of the strongest risk factors for PACG. Affected eyes are frequently hypermetropic (although not uniformly so, and PACG often occurs in myopic individuals). PACG is also associated with a short axial length, and small corneal diameter and radius of corneal curvature. Interestingly, even though PACG is more prevalent in China, one study found that Chinese, African-Americans and Caucasians had similar mean anterior chamber depths, indicating that other factors (such as the response of the iris to various stimuli) may contribute to higher rates of PACG among Chinese.

While the ocular biometric parameters described are associated with the presence of PACG and acute attacks of angle closure, it is not clear if any of them predicts which PAC suspects would have

a poor outcome if left untreated. Other important risk factors that are associated with PACG and AAC attacks are female sex, older age, and race (with Eskimo, Myanmar and Chinese populations having the highest reported rates).

TREATMENT OF ANGLE CLOSURE AND ANGLE CLOSURE GLAUCOMA

In order to review the treatment of angle closure I will discuss each of the four sub-categories separately.

1. PACS: As stated above, these individuals have no evidence of damage to the optic nerve and have a statistically normal eye pressure but have ITC when examined on gonioscopy. There is debate about how to manage such individuals with some recommending observation and others recommending laser iridotomy (LI). Two large randomized clinical trials are under way in Asia trying to answer this question.

2. PAC: All persons with PAC have ITC and the presence of either PAS or elevated IOP. There is uniform consensus that LI is indicated for these individuals to help relieve pupil block in order to both prevent acute attacks and to reduce the risk of further progression of angle closure. There are rare cases with near total PAS where iridotomy might not be indicated since it could result in an even higher IOP by overwhelming the remaining trabecular meshwork with dispersed pigment.

3. PACG: Unless PAS are extensive and there is fear of causing a substantial IOP spike while attempting LI, the first procedure for diagnosed PACG is LI. PACG is then treated like any other form of glaucoma with medications, surgery, or a combination of both. If the angle opens after LI and it is possible to perform trabeculoplasty, this is also a treatment option.

4. Primary Acute Angle Closure Attack: The mainstay of treatment of acute attacks remains medical therapy. This includes topical ocular hypotensives as well as oral or intravenous carbonic anhydrase inhibitors and in some cases hyperosmotic agents. Some have published findings that acute paracentesis can lower IOP rapidly, but this has the potential of causing damage to intraocular structures. Others have reported that laser iridoplasty can lower IOP acutely, but long-term data showing that this is more or less effective than medical therapy are not yet published. Certainly if the IOP remains elevated after one to two hours one can consider performing iridoplasty. Some have also advocated for early lens extraction once the acute attack is resolved. One study reported a lower need for medications and lower average eye pressure after lens extraction than when surgical iridectomy was performed.

Once the IOP is lowered it is important to perform laser iridotomy as soon as possible. Acute angle closure attacks have occurred in fellow eyes several hours after presentation with a monocular attack. In fact, about 10% of all acute angle closure attacks are bilateral. Therefore, performing iridotomy in both eyes as soon as possible is strongly recommended. If the cornea is cloudy in the eye undergoing the attack it is reasonable to consider pilocarpine once the eye pressure is normalized until iridotomy can be performed.

Recent publications also support primary lens extraction in some people with PACG who require IOP lowering. Some individuals have dramatic lowering of IOP after removal of the lens, even when PAS are present. Clinical trials are ongoing to determine if clear lens extraction could also be used to treat PACG.

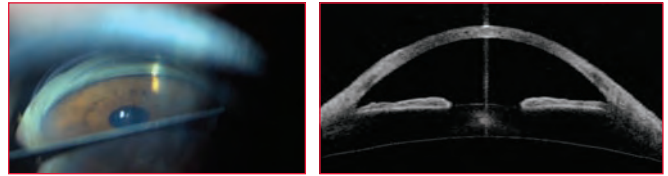


Figure 1a & b. The gonioscopic (a) and anterior segment OCT (b) image of an open angle is seen.

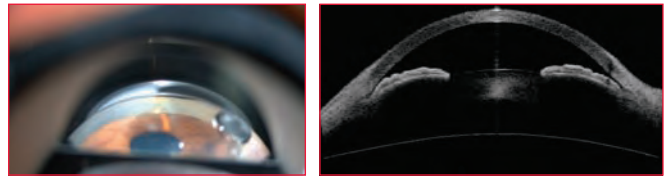


Figure 2a & b. The gonioscopic (a) and anterior segment OCT (b) image of a closed angle, undergoing an angle closure glaucoma attack is seen.

PACG is a leading cause of blindness worldwide. Gonioscopy remains the standard approach to identifying individuals at risk of this potentially blinding condition (Figure 1A and B, 2A and B). A quick and effective screening procedure is to look at the limbal anterior chamber depth (the van Herick technique). If it is less than 25% of corneal thickness there is a good chance that the angle is closed. This examination does not require any special instrumentation and can easily be incorporated into the clinical examination. Newer technologies such as the scanning peripheral anterior chamber depth (SPAC) analyzer and anterior segment optical coherence tomography may someday improve our identification of people with angle closure as indicated by a recent publication from Singapore which found that both these technologies are highly sensitive at detecting angle closure. However, gonioscopy remains the most important tool we have and is a fundamental part of the evaluation of patients seeking eyecare and needs to be performed routinely. Management of PACG is different from management of open angle glaucoma. For patients to receive proper treatment all clinicians must provide a complete evaluation of the anterior chamber angle.

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