Reducing the Pressure in Glaucoma Decision-Making

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Underdiagnosis of POAG

- Population studies suggest over half of all glaucoma patients have not been diagnosed
- From the Baltimore Eye Study: One-half of all people who were found to have glaucoma had seen an eye doctor within the past year and were unaware they had glaucoma!
- “Despite all the progress being made in the field, it is sobering that ophthalmologists fail to diagnose more than 50% of cases of glaucoma.” (Quigley, *Ophthalmology Times*)

Risk Factors For POAG

- Suspicious ONH cupping
- Elevated or increasing IOP
- Subnormal central corneal thickness (CCT)
- Advancing age (particularly after 50)
- African or Hispanic origin
  - onset earlier (about 10 years), damage more severe, treatment less successful
- Positive family history (age at Dx?)
- Diurnal fluctuation ?
- High myopia

OHTS Summary of Practice Implications

- Risk for progression of ocular hypertension to POAG can be assessed

  - Age, IOP, vertical C/D ratio, CCT
- CCT should be measured in all patients with ocular hypertension and all glaucoma suspects
- Patients at high risk should be treated
- Therapy should be selected based on efficacy, tolerability, and likelihood of patient compliance

Perspective on Central Corneal Thickness (CCT)

- CCT has become "standard-of-care" in the POAG (or suspect) work-up
- Thinner corneas are a strong risk factor for POAG because true IOP is actually higher than the measured IOP.
- Some patients with measured ocular hypertension may simply have a thicker CCT, thus reducing POAG risk because the true IOP is actually less than the measured IOP
- "CCT is the most heritable aspect of ocular structure (more than refraction, axial length, or optic disc size), suggesting that it is under exquisite genetic control." (Ophthalmology, Nov. 2007)
- "Stop adjusting IOP measurements" *JAMA, May 2017*

Corneal Thickness (µm)	Correction Value
445	7
455	6
465	6
475	5
485	4
495	4
505	3
515	2
525	1
535	1
545	0
555	-1
565	-1
575	-2
585	-3
595	-4
605	-4
615	-5
625	-6
635	-6
645	-7

Correction values for applanation tonometer readings according to corneal thickness

Calculation based on data of Ehlers et al (1975)

Modified from Stodtmeister (1998)

Arithmetic mean of corneal thickness in healthy subjects: 545 µm (Doughty and Zaman 2000)

Correction values according to corneal thickness of 545 µm

Variability of CCT Measurements

- "This study assessed the variability of central corneal thickness measurements over a single day and throughout a year in normal eyes and in eyes with primary open-angle glaucoma. The variability in central corneal thickness measurements was similar in healthy and glaucomatous eyes. Inter-day measurements exhibited larger variance than intra-day measurements."
- "Measurements of central corneal thickness are variable, with those taken on different days showing more variance than those taken on the same day. The authors concluded that a single measurement of central corneal thickness is not sufficient to accurately assess its thickness and may impact the diagnosis and treatment of glaucoma."

Published in Eye Care, Journal Scan/Research, August 28, 2017, Journal of Glaucoma

The general clinical evaluation of a new glaucoma suspect / patient

- This clinical evaluation builds upon a careful family history, personal medical history, current health status, and medication(s)
- Best corrected vision
- Document pupil size and reactivity
- Careful slit lamp biomicroscopy noting A/C depth, any iris abnormalities such as pigment dispersion, retroillumination defects, pseudo exfoliation, corneal guttata, etc.
- Applanation tonometry, noting time
- Pachymetry to determine CCT

Clinical Perspective on Rebound Tonometry

"The advantages of rebound tonometry include portability, lack of dependence on slit lamp mounting or even an external electrical source (battery powered), no need for topical anesthetic, ease of use, suitability for use by non-medically trained personnel, and toleration by young children and non-cooperative adults. These characteristics make it quite useful in screening situations. In my practice, this is our go to instrument for children as young as 3 years, for the intellectually challenged adults, and those with blepharospasm."

Reference: R. Stamper, MD, Optometry and Vision Science. January 2011

Role of Self-IOP Measurements in Glaucoma Management

- Home tonometry – logical step in understanding and management of glaucoma
- Recent FDA approvals of devices
  - » Triggerfish (Sensimed) – contact lens
  - » ICARE Home (ICARE USA) – rebound tonometry requiring no anesthetic
- Home tonometry helpful in better understanding the IOP changes and to support future glaucoma management

News on "HOME" Tonometry

- "Up to 75% of individuals have peak IOP outside of office hours."
- "Most patients (73%) were able to accurately measure their own IOP after a short training session. Self-tonometry was deemed comfortable and relatively easy to perform and has the potential to improve patient engagement in their own care."
- "Patients with glaucoma may not only find self-monitoring of IOP acceptable, but also soon demand it."

JAMA Ophthalmol, October, 2017

Glaucoma Work-Up (continued)

- Baseline gonioscopy (4-mirror preferred) looking for PAS, angle recession, angle pigmentation, and the anatomic patterns of the angle anatomy
- Thorough BIO to r/o any peripheral pathology
- Stereoscopic evaluation of the optic nerve heads (60D, 78D, or Hruby lens); glaucoma detected most often through dilated pupils
- Baseline static threshold visual fields
- Image analyzer of optic nerve head
- Optic disc photographic documentation

Optic Nerve Head Evaluation

- Cup depth is critical - Stereopsis!
- Are cup walls steep or sloping?
- Note rim translucency and vertical elongation of the cup
- Is the cup concentric with the disc, or is the cup displaced?
- Is the neuroretinal rim thinned more at certain clock hours than others? Especially look for any accentuated erosion of the inferotemporal or superotemporal regions.
- Is the disc generally pink, yellowish, or pale?

ISN'T

- Helpful diagnostic observation in ONH evaluation
- Normal neuroretinal rim anatomy follows the ISN'T rule
  - **I**nferior rim should be thickest
  - **S**uperior rim is slightly less thick
  - **N**asal rim is slightly less thick
  - **T**emporal rim should be the thinnest
- Most ONH's are round or slightly vertically oval
- ISN'T rule may not hold if ONH horizontally oval

Optic Disc Size and Glaucoma

- Bergtson (25 yrs ago)
  - Normal small discs have small cups
  - Normal large discs have large cups.
- Average disc diameter 1.5 mm

	Disc Diameter	Mean C/D	Upper Limit
Small	1.0-1.3mm	.35	.55
Medium	1.4-1.7mm	.45	.65
Large	1.8-2.0mm	.55	.75

- Implications for glaucoma diagnosis and management
  - A high ratio may not be pathologic
  - C/D's for large discs change by a smaller amount
  - C/D changes caused by glaucoma occur more slowly in large discs than in small discs (baseline photos large discs especially important
  - C/D asymmetry is not always pathological

ONH Hemorrhage

- Highly specific for glaucoma
  - RNFL/disc hemorrhages tend to be most common ST or IT.
- Prevalence higher in NTG (20-35%)
- Disc hemorrhages may precede a VF defect or a change in nerve head
- Common, but often missed, sign in glaucoma patients
- Associated with aspirin use and diabetes

(Ophthalmology 09/04)

- "Among glaucomatous eyes receiving treatment, those with a larger baseline VF defects and older age had a faster rate of VF loss after a DH developed."
- "There is no association between CCT and the later development of DH."
- "Recurrence of DH during follow-up was not associated with a fast rate of VF loss in this study."

(Ophthalmology, January 2010)

Glaucoma - Visual Fields

- Program Strategies
- Perspectives on Perimetry
- Visual Field Interpretation
  - Foundational guidelines
  - Catch trials
  - Grey scale
  - Total and Pattern deviation
  - Glaucoma hemifield test
  - Global indices
  - Summary
- Plaquenil Visual Field Testing

Ultrasummary

- A combined cerebral assessment of:
  - Pattern Deviation probability plots as compared to Total Deviation probability plots
  - Pattern Standard Deviation probability values
- These probability plots give the greatest VF data guidance to the functional status of the patient's optic nerves
- ***Remember:*** **ALWAYS CORRELATE THE CLINICAL FINDINGS WITH THE VISUAL FIELD STUDIES!**

Optic Nerve Head Image Analyzers

- GDX-VCC, OCT-3, HRT, RTA, etc.
- Can be helpful in early diagnosis
- Limited value in advanced glaucoma
- Excellent for detection of progression
- A COMPONENT of the glaucoma evaluation
- Not a “litmus test” for glaucoma

Treatment Goals For POAG

- Establish a target IOP below which optic nerve damage is unlikely to occur
- Maintain an IOP at or below this target level with appropriate therapy
- Monitor VF's and ONH appearance to refine the adequacy of the target IOP
- Optimally balance the benefits of therapy with any side effects
- Educate and engage patients in the management of their disease

Glaucoma Follow-Up

- Most controlled glaucoma patients are seen every 3 to 4 months for monitoring of the IOP and ONH status
- Visual Fields and/or a scan are done as frequently as necessary, and at least once yearly
- A dilated stereoscopic view of the optic nerve should be performed at least yearly, however, a quick look should be done at each visit.
- If control is felt inadequate, more aggressive follow-up is in order until adequate control of the patient is achieved

Glaucoma Treatment Options

- Prostaglandin Analogs
- Beta-Adrenergic Blockers
- Prostaglandin / Beta-Blocker combinations
- Adrenergic Agonists
- Adrenergic Agonist / Beta-Blocker combination
- Carbonic Anhydrase Inhibitors (CAI's)
- CAI / Beta-Blocker combination
- Pilocarpine derivatives
- Epinephrine derivatives
- Laser Trabeculoplasty
- Surgical Trabeculoplasty

Prostaglandin Receptor Agonists

- Latanoprost (Xalatan and generic) 0.005%
- Travoprost (Travatan Z and generic) 0.004%
- Bimatoprost (Lumigan) 0.01%, and generic 0.03%
- Tafluprost (Zioptan) 0.0015%

Prostaglandins

- Pharmacology: prostaglandin analog
- Mechanism: enhances uveoscleral outflow
- Dosage: once daily, usually in the evening
- Effectiveness: 30% reduction in IOP
- Potential side effects: Iris darkening, hypertrichosis, CME, iritis, HSK activation, migraine headache, inflammatory bowel disease (IBS)
- Xalatan 0.005% by Pfizer (and generic), Travatan (Z) 0.004% by Alcon, Lumigan 0.01% by Allergan, and Zioptan 0.0015% by Akorn

Latanoprostene Bunod 0.024%

- FDA approved in November 2017
- First nitric oxide – donating prostaglandin
- One molecule – two mechanisms of action
  - » Enhances uveoscleral outflow
  - » Enhances trabecular meshwork outflow
- Reduces IOP by 6 – 7 mm Hg
- Perserved with 0.2% BAK
- Used once daily in the evening (6% red eyes)
- Comes in a 5 ml opaque bottle
- Marketed by Bausch & Lomb

Each Millimeter of IOP Reduction Matters

- "Our current understanding of the relationship between IOP lowering and glaucoma onset or progression translates to the effect of each mm Hg IOP reduction on the development of progression of visual field loss."

de Moraes CG, et al. Survey Ophthalmol 2016;61(5):597-615.

"Glaucoma Treatment: by the Highest Level of Evidence"

- The risk reduction could be about 19% per mm Hg, confirming results from the Early Manifest Glaucoma Trial and Canadian Glaucoma Study, and showing that IOP reduction is highly effective, and that every mm of pressure counts.
- These results should serve as a stimulus to the pharmaceutical industry to continue development of new and even more potent drugs.

Heijl, A. The Lancet , April 5, 2015

Perspective on IOP and Progression on Glaucomatous Optic Neuropathy

- "Progression was closely linked to the magnitude of the initial IOP reduction with treatment. The initial change in IOP (from baseline to the initial follow-up visit) was strongly associated with progression, with about a 10% lowering of the risk with each mm Hg of IOP reduction."

  Leske M, et al. Arch Ophthalmol, Jan 2003

- "Elevated IOP is a strong risk factor for glaucoma progression, with hazard ratio increasing by 11% for every 1 mm Hg of higher IOP"

  Bengtsson B, et al. Ophthalmology, Feb 2007

A Look at Newer Glaucoma Medications Under Study

Rho Kinase (ROCK) inhibitor	› Relaxes trabecular meshwork › Lowers episcleral venous pressure
Norepinephrine transporter (NET) inhibitor	› Decrease aqueous production
Rhopressa (netarsudil) (ROCK/NET) (Aerie Pharmaceuticals)	› Inhibits both Rho Kinase and norepinephrine transporter › Works especially well in NTG › 0.02% Rhopressa decreases IOP 5-6 mm Hg › Dosed once daily
Roclatan (Aerie Pharmaceuticals)	› Rhopressa plus latanoprost

Bacharach J. Advanced Ocular Care, Sept 2016.

Rhopressa (netarsudil 0.02%)

- FDA approved in December 2017
- First rhokinase inhibitor
- MOA purported to be enhancement of conventional trabecular outflow
- Use once daily in the evening
- Reduces IOP about 4-5 mm Hg
- Perserved with 0.015% BAK
- Comes in a 2.5 ml bottle
- In phase III, 53% experienced red eyes
- Marketed by Aerie Pharmaceuticals

Topical Beta-Andrenergic Receptor-Blocking Drugs

- * Timolol (Timoptic and Timoptic XE / Betimol) 0.25% and 0.5%; (Istalol) 0.5%
- *Levobunolol (Betagan) 0.25% and 0.5%
- Metipranolol (Optipranolol) 0.3%
- Carteolol (Ocupress) 1.0%
- Betaxolol (Betoptic-S 0.25%)

* Have longer half-lives than other beta-blockers

Topical Beta-Blockers

- Decrease aqueous production
- Reduces IOP .25%; no response 15%
- R/O asthma
- Recommend monocular trial with lowest concentration once daily
- Possible diminished effect if used with systemic beta-blockers
- No advantage to gel-forming solution

Noncompliant Glaucoma Patient

- 66 yobm dx gl 2 yrs ago started on meds; stopped after 6 mo; father had glaucoma; DM x 10 yrs
- Meds: ASA 81 mg, atorvastatin, diclofenac, Lisinopril, glipizide, tamsulosin, Vesicare, NKDA
- BVA: 20/30, 20/20
- CCT: 520, 522
- IOP: 29, 32 8:57 am
- SLE: 2 NS OU
- Gonio: 4+ open normal pigment
- DFE: CD .7 infer thin /.8 infer thin
- VF, OCT:
- Plan:

Plan:

IOP good. Continue latanoprost qam OU. Patient has been experiencing breathing issues with full medical w/u by pulmonologist and cardiologist with unknown etiology for shortness of breath. Pulse rate today is 68 and BP 128/74 and will have patient stop timolol until f/u visit in 4-6 wks. At that time VF 24-2 SF and if IOPs up may need additional meds to latanoprost. Pt has cardiology OV in 2 wks. Pt to D/W timolol use with cardiologist. Pt to RTC 2 mo for glaucoma follow up with IOP check and repeat HVF 24-2 SF.

Adrenergic Receptor Agonists

- Brimonidine
- Apraclonidine
- Dipivefrin
- Epinephrine

Brimonidine Tartrate

- Alpha-2 adrenergic agonist; tid FDA approval
- Acts by reducing aqueous production with some enhancement of uveoscleral outflow
- Reduces IOP similar to timolol 0.5% bid
- Side effects: fatigue and dry mouth most common side effects; uveitis reported; may reduce systolic BP 10 mmHg
- Less tachyphylaxis or allergy development than the other alpha-2 agonists
- Neuro-protective potential unknown
- Alphagan (0.2%) by Allergan, and generic
  Alphagan P (0.15%) by Allergan and generic,
  and Alphagan P (0.1%) by Allergan

Combigan Ophthalmic Solution

- Combination of 0.2% brimonidine and 0.5% timolol
- With ANY combination drug, always try one of the component drugs as monotherapy, and only use the combination product if or when the monotherapy drug comes close, but does not achieve target IOP
- Remember, most all drugs have a non-response rate of about 10%, so there is a 20% chance that one of the components of any combination drug is not performing
- Marketed as Combigan by Allergan in 5, 10, and 15 ml opaque white bottles, preserved with BAK .005%

Topical CAI's

- Dorzolamide 2% sol. and Brinzolamide 1% susp.
- Mechanism: decreases aqueous humor secretion
- Reduces IOP approximately 15%
- FDA dosage: tid, practical dosage bid
- Contraindications: Allergy to sulfa and/or history of blood dyscrasias
- Side effects: minimal; some burning, bitter taste, rare allergic reaction
- Most all patients controlled with oral acetazolamide were successfully controlled with a topical CAI
- Azopt 1% susp-Alcon; Trusopt 2% sol-Merck

Dorzolamide Hydrochloride 2% – Timolol Maleate .5% (Cosopt)

- Both components decrease IOP by reducing aqueous humor secretion
- Because of the CAI, must be used bid, which results in excessive beta-blocker therapy
- Contraindications: patients with asthma, heart disease, or allergy to sulfa drugs
- Ocular side effects: burning/stinging and perversion in taste
- Marketed as Cosopt by Merck bottle and PF and generic

Simbrinza - New Combination Drug

- Combination drug without a beta blocker where both ingredient drugs are dosed the same (b.i.d.)
- Combines 1% brinzolamide (Azopt ophthalmic suspension) with 0.2% brimonidine
- Offers a wide range of treatment possibilities due to its strong efficacy and ability to decrease elevated IOP by 21- 35%
- Marketed by Alcon under the brand name Simbrinza

Contemporary Glaucoma Medication Flow

1st Tier: Prostaglandin q d or timolol q am

2nd Tier: Topical CAI or brimonidine

3rd Tier: Combigan, Cosopt, Simbrinza, or Prostaglandin/beta-blocker combination

4th Tier: Pilocarpine
Oral CAI (preferably methazolamide)