

30 Years of Clinical Challenges in Glaucoma

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No Financial Disclosures

Top 10 Countdown

It Turns Out Size Really Does Matter

3 Ways to Determine Disc Size

Measure the vertical height with a 60 diopter lens

Look at the disc area on the OCT

Eyeball estimation with a 78 diopter lens

How to Evaluate Disc Size

Use a 60 D Lens at the Slit Lamp

Make a Thin Vertical Beam

Adjust Beam Height

Read Disc Diameter off Scale on Slit Lamp

Vertical Disc Diameter > 2.2 mm Is a Large Disc

Vertical Disc Diameter < 1.8 mm Is a Small Disc

Expected Physiologic Cup Size

Based on Measured Vertical Disc Diameter

Using a 60 Diopter Lens At The Slit Lamp

	-2std	-1std	Mean	+1std	+2std
Vertical Height (mm)	1.6	1.8	2.0	2.2	2.4
Expected C/D ratio	0.0	0.2	0.4	0.6	0.8

Disc Area in the Cirrus OCT Database

Disc Area range in normal database 1.06 – 3.38 mm² (ave 1.83 mm²)

Disc area < 1.8 mm² is a small nerve

Disc area 1.8 – 2.2 mm² is a medium nerve

Disc area > 2.2 mm² is a large nerve

Redefining the ISNT Rule

ISNT Rule

Inferior>Superior>Nasal>Temporal Rim Tissue

Nasal Rim Tissue Varies Considerably Because of Blood Vessels

Glaucoma Does Not Selectively Damage Nasal Rim Tissue

Modified ISNT Rule

Ignore the Nasal Rim Tissue

Expected Ratios:

1.5-2.0x Inferior: 1.5-2.0x Superior: 1.0 Temporal

Glaucoma Should Be Suspected When the Amount of Inferior or Superior Neuro-Retinal Rim Tissue Is Equal to or Less than the Temporal Rim Tissue

Disc Size Affects the ISNT Rule

For Small Size Nerves

>2.0x Inferior: >2.0x Superior: 1.0 Temporal

For Medium Size Nerves:

2.0x Inferior: 2.0x Superior: 1.0x Temporal

For Large Size Nerves:

1.5x Inferior: 1.5x Superior: 1.0x Temporal

A New Sign of Glaucoma Damage

Who Knew We Should Look for Glaucoma Damage in the Macula?

Squeegee Sign

Glaucoma initially damages the temporal side of the ganglion cell bodies in the macula

Glaucoma asymmetrically damages between the superior and inferior ganglion cell bodies

Squeegee Sign to the superior or inferior temporal ganglion cell bodies is the initial indication of glaucoma damage on the GCA.

Ganglion Cell Analysis

Advantage of Ganglion Cell Analysis

Only available with the OCT macula scan

More reproducible measurement than peripapillary RNFL

Less physiological variation compared to peripapillary RNFL

Less major blood vessels to create pseudo-thickness measurements

Better symmetry between superior and inferior and between eyes than peripapillary RNFL

Your OCT is Flawed!!!

There are structures (ie blood vessels, astrocytes and glial cells) that contribute to the measured RNFL and optic nerve parameters by the OCT

It is difficult to create a normal data base with a structure like the optic nerve that varies significantly in regards to size, shape and number of ganglion cell axons

Errors in OCT Interpretation

Green always represents Non-Disease

Red always represents Disease

GCA artifacts

Mac edema affects GCA

ERM and VRT affects GCA

Should We Be Running More 10-2 Visual Fields?

Case ND

47 yobm c COAG OU 2* to ONH appearance OU

- Right Eye C/D: .8 thin inf rim VH: 2.0 NFL: D1 sup, D2 inf

- Left Eye C/D: .7 VH: 1.9 NFL: D1 sup, D1 inf

- IOPs s meds: OD: 16-22 OS: 18-22

- Target Pressure 15 OU

- CCT OD:610 OS:603 (thicker than average OU)

- Gonio (10.03.12):
- OD: Open to CB superior, SS all other quadrants
- OS: Open to SS 360
- (-) NVA, PAS 360 OU, flat approach to iris

c/o difficulty reading even with his reading glasses on (VA 20/20)

Predict the Visual Field Loss?

Should We Be Running More 10-2 VFs?

24-2 vs 10-2 Testing Points

24-2 tests 6 degrees apart

10-2 tests 2 degrees apart

Sita 24-2C Program

OCT GCA suggests central visual loss in glaucoma

In a standard 24-2 program only 4 points are tested in the central eight degrees

24-2C program adds 10 additional testing points to the central 10 degrees of the 24-2 program for a total of 22 testing points

Using the sita faster 24-2C program takes less testing time than standard 24-2 sita fast

Can You Predict a Glaucoma Patient's Future?

What are the Two Most Important Factors to Determine Who Will Become Visually Impaired from Glaucoma?

Amount of damage on the initial eye exam

Majority of patients that go blind from glaucoma were dx at a late stage

Age of the patient

Younger patients have more years to go blind

First Time Patient

50 yoaa male

c/o difficulty reading

Never had an eye exam

VA 20/20 OU

SL unremarkable OU

IOP 36 OD 28 OS

Gonio open angles OU

Dilate patient but

Spin the Wheel of Damage

Degree of Damage at Initial Dx

Is Early Diagnosis of Glaucoma Important?

Not for all glaucoma patients, but it is for rapid progressors

Rapid progressors can be stealth (especially with innocuous vfs despite advanced optic nerve damage)

Treatment slows down progression, but it does not eliminate progression

Our goal in glaucoma management is to keep the patient visually functional throughout their lifetime

If glaucoma is diagnosed early, there is more adequate reserve of ganglion cells to survive blindness

Age of Patient at Dx

Glaucoma More Common in the Elderly

7 X'S Greater Risk of Glaucoma in Patients Over 60 Compared to Under 40 Years of Age

However, Younger Patients Have a Longer Period of Time to Go Blind From Glaucoma

Younger Patients With Glaucoma Require More Aggressive Therapy Than an Older Patient With the Same Degree of Damage

Do We Pay Enough Attention to the Less Damaged Eye?

POAG is a bilateral disease, but is often asymmetric

The fellow eye often follows the same course as the more damaged eye, but lags many years behind

Glaucoma is a lifelong disease

Our final grade for managing glaucoma often occurs 20-30 years after the initial diagnose or when the patient passes away

The better seeing eye is more related to quality of life

Don't undertreat the fellow eye with glaucoma

Case JB

46 yobm

h/o boxing

VA 20/20 OD 20/20 OS

CF FTFC OD misses inf nasal OS

+ L APD

SL unremarkable

IOPs s meds 21-27 OD and 22-26 OS, TMax 34/37mmhg (1/2/13)

CCT 526/519

Gonio: 4+ open OU with temp angle recess OS

Should You Treat Both Eyes?

YES!

Case JB

Patient is on latanoprost, cosopt and brimonidine

Patient is s/p SLT OS

IOP on meds range 13-18 OD 13-15 OS

Would you recommend SLT OD?

Yes and set Target Pressure < 15

New G Meds: Facts and Fictions

Rhopressa (Netarsudil)

The Good

The OK

And the Concerns

Rhopressa - The Good

Aerie pharmaceuticals Rho Kinase inhibitor and norepinephrine transporter

New class of glaucoma drug

.02% concentration recommended dosage qhs

Works mainly by increasing trabecular outflow

Additive to other glaucoma medications
 Some decrease in aqueous production and lowers episcleral venous pressure
 No major systemic side effects

Rhopressa - The OK

Does not lower IOP as well as the prostaglandins
 Similar IOP lower compared with timolol, but inferior to timolol with baseline IOPs > 26

Netarsudil Is Similarly Effective with Timolol at Baseline IOPs <25 mmHg but not IOP ≥25 mmHg
 More Patients Achieve ≥20% IOP Reduction With Netarsudil vs Timolol at Lower Baseline IOPs

Rhopressa - The Concerns

Ocular Side Effects
 Hyperemia, Conjunctival Hemorrhages, Corneal Whirls, Blurred Vision

- Netarsudil QD: 22% discontinuation rate
- Netarsudil BID: 58% discontinuation rate
- Timolol BID: 4% discontinuation rate

Preferred Term (with Incidence ≥5% (Pooled Safety Population))	Netarsudil 0.02% QD (N=454) n (%)	Timolol 0.5% BID (N=459) n (%)
Eye Disorders		
Conjunctival Hyperemia	260 (57.3)	52 (11.3)
Cornea Verticillata (corneal deposits/corneal opacity)	76 (16.7)	2 (0.4)
Conjunctival Hemorrhage	81 (17.8)	4 (0.9)
Vision Blurred	38 (8.4)	8 (1.7)
Lacrimation Increased	27 (5.9)	0
Erythema of Eyelid	26 (5.7)	2 (0.4)
Visual Acuity Reduced	30 (6.6)	9 (2.0)
General Disorders and Administration Site Conditions		
Instillation Site Pain	75 (16.5)	83 (18.1)
Instillation Site Erythema	38 (8.4)	9 (2.0)

Investigations

Vital Dye Staining Cornea Present

31 (6.8)

33 (7.2)

Conjunctival Hemorrhages

Occurred in 17% of netarsudil patients

Majority 92.4% (133/144) of the conjunctival hemorrhage in netarsudil

QD group was mild, 6.3% (9/144) was moderate and 1.4% (2/144) was severe

Self-resolving with continued dosing

Corneal Whorls

Cornea verticillata refers to a whorl-like pattern of deposits typically localized to the basal corneal epithelium

Netarsudil Side Effects: Cornea Verticillata

Cornea verticillata observed (20.9%)

Resolved in 95.6% of patients after treatment ended (OBS01);

2 patients still being followed

Not associated with changes in visual function

Cornea verticillata well-studied in patients on amiodarone therapy^{1,2}

Approved 1984 USA, observed for decades

Present in >98% of patients taking standard oral dosages of amiodarone

Rarely interferes with vision

Typically reversible within 3-20 months of cessation of treatment

Cornea Verticillata Due to Phospholipidosis

Medications known to cause verticillata: amiodarone, chloroquine, naproxen, phenothiazine, ocular gentamicin and tobramycin*

Due to phospholipidosis where the parent drug is complexed with phospholipids in the lysosomes

Literature review suggested it is an adaptive response by the body rather than an adverse pathology*

Cornea Verticillata Observed in Phase 3 Studies

The onset was ~6 to 13 weeks (netarsudil QD)

Ocular AEs Leading to Discontinuations

Vision Blurred Events Reported by Subjects

Systemic Side Effects

Mean blood pressure:

– The mean changes from baseline in systolic blood pressure and diastolic blood pressure were generally small and not clinically relevant in timolol and netarsudil treatment groups

• Mean heart rate:

– Timolol reduced mean heart rate by 2.0-3.0 beats per minute

($p < 0.001$)

– Netarsudil groups did not demonstrate significant reductions in mean heart rate

Most Frequently Reported Systemic TEAEs

Systemic (non-ocular) adverse events reported in $\geq 2.0\%$ of subjects by treatment group (Safety Population)

The Final Concern

Cost

Rocklatan

Combination of Rhopressa and Latanoprost

Dosed once a day

34% IOP reduction

2 mm additional IOP reduction than latanoprost alone

Hyperemia the major side effect

Vyzulta™ (latanoprostene bunod ophthalmic solution), 0.024%

Bausch+Lomb

.024% concentration

Combination of latanoprost and a nitric oxide donor

LBN is rapidly metabolized in the eye to latanoprost acid and butanediol mononitrate

Nitric oxide relaxes the TM and ciliary muscle increasing trabecular outflow

Latanoprost lowers IOP by increasing uveal scleral outflow

Vyzulta lowers IOP 1-2 mm more than latanoprost alone

Latanoprostene Bunod has a Dual Mechanism of Action

APOLLO and LUNAR:

Change from Baseline by Visit (ITT, LOCF)

VOYAGER: Latanoprostene bunod 0.024% Led to Greater IOP Reductions Compared to Latanoprost at All Study Visits

The most common ocular adverse reactions observed in patients treated with Vyzulta™ (n=811, across both studies) were

conjunctival hyperemia (6%)

eye irritation (4%)

eye pain (3%)

instillation site pain (2%)

Approximately 0.6% of patients discontinued therapy due to ocular adverse reactions including ocular hyperemia, conjunctival irritation, eye irritation, eye pain, conjunctival edema, vision blurred, punctate keratitis and foreign body sensation.

What is the New Paradigm for Glaucoma Treatment?

Glaucoma Management 2019

Start with a prostaglandin qhs or Vyzulta qhs

Add Beta-blocker bid

Change beta-blocker to Cosopt bid

SLT or Add Rhopressa qhs as a third drug

Add Alphagan bid as fourth drug
Filtering surgery
Only if the benefits outweigh the risks

What about MIGS? (10 minutes)

MIGS vs MEGS and Name Changes
MIGS - Minimally Invasive Glaucoma Surgery
MEGS - Minimally Effective Glaucoma Surgery

“Lies, Damn Lies and Statistics”

Quote from Mark Twain in reference to the use of statistics to bolster weak arguments
Most MIGS procedures are done in conjunction with cataract surgery
Most Pro-MIGS lecturers will quote:
“According to the AAO Preferred Practice Patterns, cataract surgery with IOL implantation alone results in a modest reduction in IOP of less than 2mm Hg on average.¹”

¹American Academy of Ophthalmology, Preferred Practice Patterns, 2010.

Effect of Cataract Surgery on IOP Reduction

In studies that are compared with cataract surgery vs cataract surgery + MIGS, data is rarely reported as the IOP lowering between the two groups.
Success is defined by the authors as a 20% IOP reduction. Cataract surgery alone gets you a 20% reduction in 50% of patients. The other 50% are probably very close to achieving that threshold, so if the MIGS gives you another 1-2 mm reduction you will achieve a success. Comparison is also reported by the reduction of glaucoma medications which can also be misleading because of the minimally additive effect of multiple glaucoma meds and defining a threshold of 21 mmHG as a need for medication.

Not All MIGS are Created Equal

Less Invasive – Less Effective

Endoscopic Cyclophotocoagulation (ECP)
I Stent
Hydrus Microstent
Canaloplasty

More Invasive – More Effective

Trabecutome
Suprachoroidal Stents (Cypass)
Xen
Express Shunt (trabeculectomy)

Endoscopic Cyclophotocoagulation (ECP)

810-nm diode laser on a 19-gauge endoscopic probe.
Laser procedure to the ciliary body typically performed during cataract surgery
A 180°ECP treatment at the time of cataract surgery can reduce the IOP by 10% to 15%, an effect that will last at least 3 years.
Complications inflammation, CME and potential hypotony

Glaukos iStent

Ab internal micro titanium device

Inserted through the trabecular meshwork into Schlemm canal during cataract surgery

Glaukos iStent

Samuelson et al Ophthalmology 2011;118:459-467

240 eyes randomized to cataract surgery vs cataract surgery with iStent

12 month follow up

Mean IOP reduction in iStent was 8.4 mmHG vs 8.5 mmHG in the control group

Mean reduction in eye medications 1.4 meds in iStent vs 1.0 meds in control group

66% of iStent eyes vs 48% of control group achieved an IOP reduction of 20% without medications at 12 months

At 24 months, these proportions had declined to 53% and 44%, and this difference was not statistically significant.

4% stents become obstructed with iris, vitreous, fibrous overgrowth

3% become malpositioned

1% need to be removed

Glaukos iStent

Craven et al J Cataract Refract Surg 2012;38:1339-1345

Prospective randomized controlled multicenter clinical trial

240 eyes with mild to moderate glaucoma randomized to cataract surgery or cataract surgery + stent

IOP reduction of 20% without meds 61% in the stent group vs 54% control group

At 24 months the IOP in the stent group was 17.1mm on .3 medications and in the control group 17.8 mm HG on .5 medications

There was no difference in safety prolapse between the two groups

Glaukos iStent

Long term results (Arriola-Villalobos, BrJOphthalmol 2012;96:645-649)* authors had no commercial or proprietary interests

19 patients

Combined cataract surgery and iStent

Minimum 3 year follow up (ave 54 months)

IOP reduced from 19.42 to 16.26 mmHG (16% reduction)

Meds reduced by .5 medication

Not a randomized clinical trial so no control group to compare results

21% had malpositioned stent

11% had partially occluded stent with PAS

Dorairaj et al A multicenter retrospective comparison of goniotomy versus trabecular bypass device implantation in glaucoma patients undergoing cataract extraction. Clinical Ophthalmology Feb 2019.

I Stent vs Goniotomy

Mean IOP reduction from baseline was significantly greater in the phaco-goniotomy with KDB group at Month 6 (phaco-goniotomy with KDB -4.2 mmHg [23.7%] vs phaco-iStent -2.7 mmHg [16.4%]; P,0.001).

IOP-lowering medication reduction was greater in the phaco-goniotomy with KDB group compared to the phaco-iStent group (1.1 vs 0.9 medications, respectively; P=0.001).

The most common adverse event was IOP spikes occurring in 12.6% of phaco-iStent eyes and 6.3% of phaco-goniotomy with KDB eyes (P=0.024).

Cost and Reimbursements

Cost of the iStent \$1,000
2013 Medicare facility reimbursement \$2,978
Ambulatory surgery center reimbursement \$1,671
Average physician fee \$850

Hydrus II Microstent Study

100 glaucoma patient with mild to moderate disease randomized to cataract surgery with or without Hydrus II Microstent
11 months after surgery
Treatment group had IOP 16.0 on .4 meds
Control group had IOP 15.8 on .9 meds
No major adverse effects reported

HORIZON Study

A total of 369 eyes were randomized after phacoemulsification to Hydrus Microstent (HMS) and 187 to no microstent (NMS).

At 24 months, unmedicated MDIOP was reduced by $\geq 20\%$ in 77.3% of HMS group eyes and in 57.8% of NMS group eyes (difference = 19.5%, 95% confidence interval [CI] 11.2%-27.8%, $P < 0.001$).

The mean reduction in 24-month unmedicated MDIOP was -7.6 ± 4.1 mmHg (mean \pm standard deviation) in the HMS group and -5.3 ± 3.9 mmHg in the NMS group (difference = -2.3 mmHg; 95% CI, -3.0 to -1.6 ; $P < 0.001$).

The mean number of medications was reduced from 1.7 ± 0.9 at baseline to 0.3 ± 0.8 at 24 months in the HMS group and from 1.7 ± 0.9 to 0.7 ± 0.9 in the NMS group (difference = -0.4 medications; $P < 0.001$).

15% of HMS developed PAS in the angle and 4% of HMS developed obstruction of the stent opening

Canaloplasty

Trabectome

Suprachoroidal stent

Cypass Stent
Cypass Recall
IOP Reduction
>30% ECL
ECD < 1500 cells/mm²

Xen

Ab Interno Sub-Conjunctival Drainage
Really a type of filtering surgery

Express Shunt

Trabeculectomy

Advanced glaucoma damage
Achieve low target pressures
Control IOP spikes

Less reliance on patient's taking their medications

What are the drawbacks of filtering surgery

In skilled surgeon hands, it is still only 80% successful

IOP is often higher in a failed filter than before the surgery

Accelerate cataract formation

More local foreign body sensation

Risk of catastrophic complications

The Safest Cost Effective MIGS is Cataract Surgery

Cataract surgery lowers IOP 2-7 mmHG

Clear cornea phaco lowers IOP greater than extracapsular cataract extraction

Effect is long lasting

80% maintained 3 mmHG IOP lowering for 5 years