Hodgepodge of the Eye
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Southern College of Optometry
Illinois Optometric Association – September 15, 2019

Retina Brainteaser Cases...
Chris Borgman, OD, FAAO

COPE Disclosures:

• I do not have any relevant financial relationships to disclose.

• The content and format of this course is presented without commercial bias and does not claim superiority of any commercial product or service.
Ground Rules...

• Don’t look ahead!
• I’m not perfect...
• Some cases are more straight forward than others...
• I will email you my reference list if you want it....

• Email: cborgman@sco.edu

Case #1:

“Why does my uveitis keep coming back?”

Case History...

• 38 year old AF
• History of recurrent iritis q6 months x 2 years OS only
• Vietnamese immigrant; non-English speaking
• POH: (+)phaco OS 18 months prior secondary to PSC
• PMH: denies all
• FMH: unknown
• SH: unremarkable
• ALL: NKMA/NKDA
Exam...

• VA = 20/20 OD, 20/30+ OS (sc)
• EOM’s/Pupils/CVF = WNL OU
• Adnexa = WNL
• Slit Lamp = OD WNL, OS had old corneal KP’s, no current A/C rxn, stable PCIOL OS with no PCO
• IOP = 16 mmHg, 15 mmHg with Goldmann
• DFE: see pictures
Labwork ordered.....

- CBC with diff = WNL
- ESR = WNL
- RF = WNL
- ANA = WNL
- PPD = WNL
- Chest x-ray = WNL
- ACE, lysozyme = WNL
- Lyme titers = non-reactive
- RPR = WNL
- FTA-ABS = negative
- HIV = WNL
- Toxocarasis titers = WNL
- Toxoplasmosis titers = IgG reactive, IgM non-reactive

Toxoplasmosis Iritis....

- Intracellular infection of the intracellular parasite Toxoplasma gondii
- Recurrent posterior uveitis, usually unilateral
- 90% posterior uveitis = toxoplasmosis
- See = floaters, blurry vision, pain, photophobia, veils, etc.
- Sx = iritis, vitritis, retinochoroiditis, retinal scars
- Most common onset = 20-40 years of age
- Posterior pole = 50% of cases

- Optic nerve involved in 15% of cases
- Aka = "toxoplasma neuroretinitis"
- HIV patients at highest risk when CD4 <250
- USA = 40% exposed
- Europe, Asia, Africa, S. America = 40-80% exposed

T. Gondii Life Cycle...

- T. Gondii life cycle:
  - Cats = definite host (needed)

- Humans more than likely get it from undercooked meat and/or contaminated drinking H2O

- Direct exposure from cats themselves is possible but rarer...
T. Gondii Treatment...

• Observation only in most cases...

• If macula/ONH/vision threatened then Tx is indicated...

• Vision Threatening Defn: any lesion within temporal arcades or adjacent to ONH

1. "Classic therapy" (pyrimethamine, sulfadiazine, prednisone)
   • Pyrimethamine can cause: leukopenia and thrombocytopenia, GI problems, dermatological problems too; hence #2 most common Tx now

2. Trimethoprim/sulfamethoxazole (Bactrim) and oral prednisone

3. Clindamycin and prednisone

• Note: Topical steroids (Pred Forte, Durezol) still important for anterior uveitis

T. Gondii and mental illness?

Several newer studies have been linking mental disorders such as schizophrenia, suicidal thinking, depression, and other neuropsychiatric disorders with T. gondii...

Dr. Brian Hall——“Maybe there is some truth in the stereotypes of the crazy cat ladies.”

Ocular Toxoplasmosis Prevention...?

• Similar concept to recurrent HSV...

• Trimethoprim/sulfamethoxazole (160-800 mg) PO q3 days

• Decreased recurrent episodes from 23.8% to 6.6% over 20 month period

• Viewed as best with history of recurrence and/or scars adjacent to the fovea

• Promoting resistance???
Consider prophylactic Tx here???

Case #2:
“Doc, I can’t see very well...”

Case History...
HPI: onset 5 days, OS>OD, D & N, h/o trauma with coat hanger
5 days earlier OS, (+) floaters/flashes OS>OD
POH: LEE 6-8 months; current Rx 2 months old
PMH: LME >4 years, (+) arthritis, (+) Sickle Cell (SC variant)
Meds: denies, vitamins only
Allergies: PCN
SH: unremarkable
Exam...

- **VA:**
  - OD 20/50 - (PHNI)
  - OS 20/60 - (PHNI)
- **EOM:** FROM OU
- **CVF:** FULL OU
- **Pupils:** equal, round, RL 4+ OU, (-)APD OU
- **SLE:** unremarkable OD, OS
- **Tonometry:** 14 mmHg OD, 13 mmHg OS
- **DFE:** see pics

DFE...

SC Trait vs. SC Disease

- **AA** = normal
- **AS** = trait
- **AC** = trait
- **SS** = sickle cell disease (anemia)
- **SC** = sickle cell disease

- Spectrum of SCD: 80% AS, 4% SS, 2% SC, 14% other types
Sickle Cell Disease (SCD)

- Inherited disorder of Hemoglobin molecules
  - Most common hemoglobinopathy
- 60,000 people in U.S. with SCD (not trait)
- 8.0% of African Americans have sickle cell trait (AS)


Hemoglobin Review

- Normal Hemoglobin:
  - 2 α-chains and 2 β-chains
  - Hemoglobin A = normal “adult”
  - Lifespan of 120 days
- Sickle Cell Hemoglobin:
  - Different combos of β-chains; α-chains are unchanged
  - β-chains are reduced/missing = Thalassemia
  - Hemoglobin S = abnormal
  - Hemoglobin C = abnormal
  - Lifespan of 16 days
  - Cleared by spleen much more quickly →severe anemia

Pathogenesis of SCD

- Low O2 environments →“sickling” → sticky → vascular occlusions
  - Point mutation on hemoglobin β-chain
  - Glutamate is replaced by Valine = SS
  - Glutamate replaced by Lysine = SC
  - Hb loses O2 → Valine/Lysine binds to open spot in molecule forming long rigid strands → sickle shape
  - Occlusions cause tissue ischemia throughout body leading to various complications
Laboratory Testing

1. **Sickledex test (screen)**
   - Identifies presence of Hb S (99% accurate)
   - Sickle Cell Trait --- may be NEGATIVE
   - May be masked by normal Hb A molecule (rare)

2. **Hemoglobin Electrophoresis**
   - Performed if Sickledex is positive or inconclusive
   - Capable of identifying:
     - Hb AA
     - Hb AC
     - Hb AS
     - Hb SS
     - Hb SC
     - Hb Sthal variants

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**SC Retinopathy: Stage 1 (Non-Proliferative)**

1. Peripheral Retinal Arteriolar Occlusions
2. Salmon Patches (fresh intraretinal hemorrhages)
3. Black Sunbursts (resorbed hemorrhages associated with RPE hyperplasia)
4. Venous Tortuosity
5. Angioid Streaks (rarely can develop CNVM)

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**SC Retinopathy: Stage 2 (Non-Proliferative)**

- Arteriovenous anastomosis
- Shunt vessels
- Arterioles → Venules
SC Retinopathy: Stage 3 (Proliferative)

- VEGF released from the retina in response to ischemia
- Seafan neovascularization proliferates
  - Most common in superior-temporal quad
  - Very similar to PDR in diabetics
- Tx: PRP laser to non-perfused retina, direct laser to feeder vessels and/or neo
- Alternate Tx: Avastin injections
- According to Massachusetts Eye and Ear Infirmary, 60% of seafan neo spontaneously regresses on its own...

<table>
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<th>Risk of Converting to Vitreous RD from Stage 3</th>
<th>Timeframe</th>
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<tr>
<td>5.1%</td>
<td>6.3 years</td>
</tr>
<tr>
<td>2%</td>
<td>6.3 years</td>
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SC Retinopathy: Stage 4 (Proliferative) --- Vitreous Hemorrhage

- Risk of Vitreous Hemorrhage:
  - SC—21-23%
  - SS—2-3%
- Results from fibrous tissue traction on seafan neo which breaks and leaks into vitreous
- Tx: Usually monitored for 3-6 months. Non-clearing or sight-threatening → PPV

SC Retinopathy: Stage 5 (Proliferative) --- Retinal Detachment

- Stems from fibrous scaffolding of seafan neovascularization which contracts/pulls on retinal tissue—RD
- Tx: RD repair surgery (scleral buckle, laser, cryotherapy)
- Scleral buckle in SCD has 70% chance of anterior segment necrosis
  - Non-SCD has only 5% chance
- Prognosis guarded (depends on location, extent, etc.)
Systemic Complications

• Any one of these alone or in combo could be called “sickle cell crisis”

• Organ Infarcts:
  • Lungs → pulmonary embolism
  • Spleen → increased risk of infection
  • Kidney
  • Liver → jaundice
  • Anemia
  • Gallstones
  • Stroke/CVA
  • Joint Pain
  • Arms, Legs, Chest, Abdomen
  • Can be severe

Current Systemic Tx Options

1. Pain Relievers—joint and bone pain
2. Blood transfusions—replaces defective RBC’s, only cure available
3. Antiplatelet therapy—decreases risk of clotting
4. Anticoagulation—decreases risk of clotting
5. Thrombolytic agents—clear already blocked vessels
6. Gene Therapy—replacing defective Hb chains; area of research
7. Nitrous Oxide—induces vasodilation
8. Hydroxyurea—increases production of Hb-F via transcription
   • Hb-F has higher affinity for O2
   • Decreases chances that RBC’s will sickle in low O2 environment

Hydroxyurea (HU) Therapy

• Harminder et al. found that Hb-F was increased from 12.83% to 19.17% in one year
  • 20-25 mg/kg once daily dosing
  • Mean overall Hb levels increased from 9.15 g/dL to 9.98 g/dL

• Conclusion:
  • HU treatment resulted in ↑Hb-F levels, ↓SCD crisis, ↑ intervals between blood transfusions, and ↓hospital admissions.
  • Authors suggest increasing acceptance of HU therapy
  • Concurrent use of transfusions as needed

• Other studies w/ hydroxyurea therapy:
  • Tx resulted in 10 year survival of 86% vs. 65% of no-Tx
Back to the patient....

- Sickle cell SC ➔ highest risk of retinopathy
- Set up with retinal specialist who recommended PPV OU
- Patient no-showed to surgery date
- Has not returned calls/letters
- "Unless your patient is too young or cognitively impaired to know better, you can’t care more for him than he cares for himself."
  - Drs. Joe Sowka and Alan Kabat

Shameful plug, I know!


New Case: 39 YO AAM
What is going on here?
Persistent Fetal Vasculature...

- **Defn:** Failure of hyaloid vasculature to undergo programmed involution
- **Anterior, posterior, combined forms**
- **3% of all full term infants have some form of PFV**
- **MOA:** Dysregulation of apoptosis
  - **Unilateral (89-98%)**
  - **Bilateral (2-11%)**
  - The nomenclature changed from PHPV to PFV in 1997
    - Reflects the inclusion of pathology throughout this system:
      - Vasculature
      - Iris
      - Lens
      - Vitreous
      - Retina
      - Macula
      - Optic nerve

Case #3:

“Doc, my vision is patchy...”

Case History...

- **31 YO WF**
- **CC:** “blurry/patchy vision” OD>OS, onset 3-4 weeks, spots missing in vision OD>OS, sudden onset
- (-) DM, (-) HTN, (-) tobacco
- LME = unknown, long time per pt
- (-) head, chest, or ocular trauma, (+) broken femur
- Meds = oxycodone PRN, Ca pill, Vit D
- ALL = NKMA
Exam...
- VA = 20/20 OD, 20/30 OS, PHNI OS (sc)
- EOM's = WNL
- Pupils = WNL
- CVF = WNL
- Amsler = “patchy” vision paracentrally L > R
- MR: OD plano 20/20 slow
  OS pl – 1.00 x 090 20/20-2 slow
- SLE: WNL OU
- IOP = 16 mmHg OU
- DFE: see pics

DFE...

Labwork....
- CBC with diff, ESR, FBS, HbA1c, ANA, RF, ANCA, RPR,
  Hepatitis panel, HIV, ANA, Lyme titer, BMP, thyroid panel,
  lipid panel, Protein S & C, ANCA, anticardiolipin,
  antiphospholipids, PT/PPT

- ALL WNL!!!

> Remember, patient had femur fracture from
  football accident 3-4 weeks prior...
Purtscher-like Retinopathy...

- Purtschers Retinopathy = retinal hemorrhages, CWS, ONH edema in patients with severe head trauma or compressive chest trauma
  - 83-92% cases have intraretinal hemorrhages & CWS
  - When non-traumatic case → "Purtscher’s-Like"
- Average age = 34 YO
- 60% male
- 60% bilateral, 40% unilateral
- Sx start within 24-48 hours to 2 days usually
- VA = 20/20 → NLP reported
  - Central scotoma in 93% cases
  - Paracentral > arcuate > peripheral

Purtscher’s-Like Retinopathy Potential Causes...

- Acute pancreatitis
- Pancreatic cancer
- Renal failure
- Autoimmune diseases
- Pregnancy complications (preeclampsia, HELLP, amniotic fluid embolus, etc.)
- Multiple Myeloma
- Thrombotic Thrombocytopenia purpura
- Childbirth
  - Long bone fractures
    - Femur, shoulder joints

Pathophysiology?

- MOA: truly unknown...
  - Leading theory ➔ pre-capillary arteriolar occlusion due to embolization from air, granulocyte, fat, platelets, fibrin other leuko-aggregates formed after complement activation
  - Noticeably, visible retinal emboli are absent!
  - Air emboli from chest compression syndrome
Fat Emboli? How?

- Systemic embolism may stem from:
  - Patent foramen ovale
  - AV pulmonary shunts/malformations
  - Persistent ductus arteriosus

- “Fat emboli are commonly released from the intramedullary fat into the venous circulation after long bone fracture, surgery, and pancreatitis...such emboli would be more likely to occlude the smaller 5 µm retinal capillaries at the time of injury.”— Agrawal & McKibbin (2006)

- Fat emboli = 5-10 µm
- Precapillary arterioles = 45 µm
- Retinal capillaries = 5 µm

Management...

- FANG ➔ Arteriolar occlusions
- ICG ➔ Evidence for choroidal hypoperfusion

- Follow up:
  - 1 month
  - 2-3 months
  - 6-12 months

- Treatment:
  - Monitor
  - Resolution in 1-3 mo typically
  - Corticosteroids (no statistically significant difference in studies)
  - Hyperbaric oxygen

Back to patient...

- Failed to return as directed...
- Did see retinal specialist who confirmed PLR
Case #4:
“Doc, I don’t feel so good...”

Case History...
- 43 year old WM
- Referred for vision loss and HA after being admitted to hospital, onset 1 week, OD > OS, D = N
- LME = doesn’t remember; long time ago
- BS = 600+
- HbA1c = 18.6%....wow!
- BP = 200/120
- Also, hypertriglyceridemia and hypercholesterolemia
- CT/CTA = WNL OU in emergency room

Exam...
- BCVA = 20/50 OD, 20/20 OS
- EOM’s = WNL OU
- Pupils = PERRLA, (+)mild APD OD
- CVF = WNL OS, inf nasal restriction OD
- HVF = WNL OS, central and inf nasal defects OD
- Adnexa/SLE = WNL OU
- DFE: see pictures
- IOP = 19 mmHg OU via Goldmann
- ESR and CRP = WNL in ER department work-up
OCT that day...

Signal Strength:
OD 8/10
OS 9/10
OD avg = 313 μm
OS avg = 84 μm

Diabetic Papillopathy...
- Defn: optic disc edema in a DM patient with minimal or mild optic nerve dysfunction
- Some suggest is on mild end of NAION spectrum
  - Typically more peri-papillary hemorrhages than NAION
- 70% have Type 1 DM
- 60% are unilateral; 40% bilateral
- No specific Tx for edema; treat DME if present; spontaneous recovery usually occurs over several weeks to months
- May have permanent visual field or acuity defects
- Control underlying systemic issues (BS, BP, BC, etc.)
- FANG can differentiate between DM papillopathy and NVD
  - Rarely needed...
Back to patient…

• Sent to retina given proximity of exudate and CWS to macula…
• FANG ruled out CSME → retina chose to monitor
• Patient returned 2 months later
  • VA = 20/25-2 OD, 20/20 OS
• Dramatically improved optic nerve swelling on OCT and exam
• Monitor q6 months given BS levels

2 months later…

Signal Strength:

OD 8/10
OS 8/10

OD avg = 90 μm
OS avg = 84 μm

Case #5:

“Doc, I can’t breathe very well...”
Case history #1...

- 64 year old white female
- "Vision...is...blurry...OS...I can’t breathe very well..."
- Stopped exam → sent patient to ER in wheelchair

Case History #2....4 weeks later

- Chest CT in ER showed numerous masses → stage 4 lung cancer
  — Smoker x 50+ years, 1-2 packs/day
- Full body scans revealed metastasis to liver, brain, brainstem, neck, chest, spine, and abdomen → EVERYWHERE!
- Refused chemo, started radiation

Choroidal Metastasis OS

— Sup/Temp with exudative RD involving fovea

Choroidal Metastasis...

- Women > Men (70%-30%)
- Average age = 50-60 years of age
- Men = Lung Cancer
- Women = Breast Cancer
- Most common intraocular malignancy
- Usually amelanotic, shallow, oval/round mass
  - "leopard spots" = macrophages containing lipofuscin
- 90% are posterior to equator of eye!........why?
- Choroid is highly vascularized!
- Less than 10% have metastasis from sites other than lungs or breasts
- Sx = blurred vision, floaters, VF defects, metamorphopsia, asymptomatic
- SRF and serous retinal detachments are found in 91% of cases
- History of malignancy in 65-75% of patients
Types of Retinal Metastasis...

- **Choroid is most common site of metastasis to eye**
  - Breast carcinoma = 39-49% of uveal metastases
  - Lung carcinoma = 21-29%
  - GI Tract = 4%
  - Kidney, skin (melanoma), prostate, pancreas, thyroid, testes ...

- In 17-18% of cases the primary metastasis site remains unknown

- "Ocular ultrasound is really important with metastases because they tend to be echogenic, whereas melanoma tends to be echolucent."
  — Carol Shields, MD (Wills Eye Hospital)

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Most important differentials...

- Amelanotic choroidal melanoma/nevus
- Choroidal hemangioma
- Lymphoma
- Choroidal osteoma
- Disciform macular scarring
- Posterior scleritis
- CHRPE
- Rhegmatogenous RD

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Is color of mass important?

- Some tendencies but not specific in all cases...
  - Pale-yellow = lung/breast cancer
  - Dark grey/Brown = cutaneous melanoma
  - Orange/red = renal cell or thyroid carcinoma
  - Pink/Yellow-orange = carcinoid tumors
Choroidal Metastasis Treatment...

- **Ocular:**
  - External-beam radiotherapy
  - Chemotherapy
  - Hormonal therapy
  - Plaque radiotherapy
  - Enucleation
  - Any combination of the above

- **Systemic:**
  - Left to oncologist...radiation, chemotherapy, surgery, etc.
  - Sometimes ocular tissues are simply monitored for response to systemic treatment
  - Life expectancy strongly considered too!

Prognosis...

- Ocular metastasis carries an exceedingly poor systemic prognosis...
- Life expectancy = **12-21 months** (gross mean)
- Bleak outlook overall...

- Ocular oncology referral

Back to the patient...

- Patient declined chemotherapy, agreed with radiation Tx
- Referred to local retina specialist too...
- Given spread to entire body specialist wanted to monitor with systemic treatment only first given bleak outcome
- Patient died 4 months later...
Case #6:
“Doc, I feel great and don’t have any problems...”

Chief Complaint:
- 10 YO AAF; First eye exam ever
- Failed school screening
- Referral said OD>OS blurriness
- Patient denied any difficulties with vision
  - A's and B's for grades; “does very well”
- Father had never noticed any problems before

Case History
- POH: (-)injuries, (-)surgeries, (-)strab, (-)Rx before, (-)trauma
- PMH: denies all, sees PCP yearly, full term baby with no problems during delivery, normal milestones
- FOH: (+) grandmother with borderline POAG
- FMH: denies all
- MEDS: denies all
- ALL: NKMA, NKDA
Ocular Exam Continued...

Refraction:  
OD: +1.50-1.50x180  
OS: +0.75 sph  
20/80  
20/20

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<td>Angles</td>
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<td>A/C</td>
<td>D &amp; Q</td>
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<td>Clear, Brown</td>
<td>Iris</td>
<td>Clear, Brown</td>
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<tr>
<td>Clear</td>
<td>Lens</td>
<td>Clear</td>
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Tonometry: 20 mmHg OU via Goldman
Choroidal Rupture

- Tear in choroid, Bruch’s membrane, layers
- Typically follows blunt trauma
  - 5% of time; M>F
- May acutely be covered by hemorrhage or commotio retinae (Berlin’s Edema)
- Yellow or white crescent shaped streak
- Concentric to optic nerve

Rupture Mechanism of Action

- Two Types of Choroidal Rupture:
  1. Direct — site of injury, usually parallel to ora serrata, more anterior
  2. Indirect — contrecoup injury, typically posterior pole, “classic rupture”

Choroidal Rupture Complications...

- CNVM
  - Occurs in 5%-10% of rupture cases
  - Months to years after trauma (up to 37 years) (avg 7-8 months) (81% within one year)
  - FANG/ICG and/or OCT to help with Dx
  - Usually anterior to RPE in neurosensory space
- Scar Tissue of Retina/Rupture Site
  - Fully scarred 3-4 weeks after trauma
  - Usually have to wait for hemorrhages to reabsorb in order to have clear view
Choroidal Rupture Treatment...

1. Monitor with Amsler Grid
   • q6-12 months
   • No Tx if no CNVM

2. Laser Photocoagulation
   • Juxtafoveal and extrafoveal CNVM

3. Photo-Dynamic Therapy
   • Subfoveal CNVM

4. Surgical Removal of CNVM
   • Subfoveal CNVM

5. Anti-VEGF Agents (Avastin, Lucentis)
   • Subfoveal CNVM

Choroidal Ruptures and Final Visual Acuity

• Ament et al. studied 111 indirect ruptures (2006)...
• Final Acuity Results ≥1.5 Years:

<table>
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<tr>
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<th>Peripheral CR</th>
<th>Macular CR</th>
<th>+ CNVM</th>
<th>- CNVM</th>
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<td>Total [n]</td>
<td>34</td>
<td>75</td>
<td>19</td>
<td>12</td>
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<tr>
<td>Final VA ≥ 20/40</td>
<td>59%</td>
<td>22%</td>
<td>38%</td>
<td>8%</td>
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- CNVM Likelihood: older age, length of CR (not width), macular rupture location
- Poor Prognosis with: macular rupture location, (+) CNVM, ↓ baseline VA

Traumatic Macular Holes...

• 83% macular holes are idiopathic
  • Tend to be gradual formation over weeks to months

• 5%-15% holes due to trauma (TMH)
  • Coincide with traumatic event; immediate formation

• 95% achieve hole closure with surgery
Mechanism of Action...

- Very similar to choroidal rupture MOA
- Anteroposterior compression of globe → stretches retinal tissues

2 Theories:
1. Immediate Tear of Retina — immediate hole upon trauma
2. Tangential Vitreous Traction — delayed/slow hole formation

Treatment:
- PPV with Fluid-Gas Bubble Exchange
- "Tamponade"

TMH Monitoring Only Outcomes...

- Yamashita et al. studied 18 total eyes with TMH
- 44% showed spontaneous closure within 8.4 months (Japanese studies)
- Other 2 studies show range of 10-67% spontaneous closure of TMH
  - Final VA same as with surgery

Problem: Which pts will close spontaneously?

TMH Surgical Outcomes...

- Yamashita et al. combined 2 studies (39 eyes total) (2002)...
  - 95% achieved hole closure with surgery
  - 77% had final VA of ≥20/40
  - Surgery = faster closure of hole
  - Surgery has no effect on final VA
  - Monitor for several months in acute setting then surgery for traumatic macular holes
  - Chronicity may play a role as well
Patient outcome...
- Sent to retinal specialist.
- Declined further surgery given lack of clear timeline of trauma
- Youngest of 7 children.
- Vaguely remembers trauma with roller skate to same eye as a child at the hands of an older sibling.
- (-) CNVM----------Tx = monitor only
- Polycarbonate for protection at all times
- Be aware of child abuse in odd cases like this.

Shameful Plug....again...

Case #7:

“Doc, I have this occasional flash in my eye.”
Exam...

- 53 YO AF (Vietnamese migrant) (limited English)
- CC: “mild flashing lights” OD, onset few years, worse when bending over, (+)PVD in previous records OD
- PMH: denies, LME 6 months prior
- FMH: (+)HTN
- SH: unremarkable
- Meds: BC pill
- ALL: NKMA

VA = 20/20 OD, 20/20 OS (cc)
- EOM/Pupils/CVF = WNL OU
- SLE = mild pinguecula OU temporally
- Tonometry = 15 mmHg OD, 14 mmHg OS with Goldman
- DFE = see pictures...
Huh? What is going on here?

• Biggest differential Dx = Cotton Wool Spot

• "Myelinated nerve fiber layers can be confused with cotton wool spots...If uncertainty persists, photograph the lesion and reappoint the patient for re-evaluation. Cotton wool spots fade over several weeks, whereas myelinated nerve fiber layers do not."
  • The Handbook of Ocular Disease Management: 10th Anniversary Edition. Review of Optometry; April 15, 2008; 464-474.

NFL Myelination...

• "Normal myelination typically progresses from the chiasm to the optic nerve from the eighth month of gestation until birth and then stops at the lamina cribrosa." --- Shelton JB, et al. JAMA Ophthalmol. (2013)

• Congenital mainly
• Progression/Regression has been documented too

Case #8:

“Doc, I need my DOT form filled out today.”
Case History...

- 38 year old WF
- CC: “failed my DOT test and need this form filled out”
- “Vision OD is fine but my OS is bad” (stable for years)
- DOH: OS has been bad since car accident when she was 1-2 YO
- PMH: unremarkable
- FMH: unremarkable
- Meds: denies
- ALL: NKMA/NOKDA

Exam...

- 20/20 OD, 20/HM OS (PHNI)—cc
- EOM's = WNL OU
- Pupils = mild APD OS
- CVF = WNL OD, some nasal hemifield difficulty OS
- Adnexa/SLE = WNL OU
- IOP = 11 mmHg OD, 13 mmHg OS
- DFE: see pictures

- Refraction:
  OD -4.75 -1.25 x 090 20/20
  OS +/-6.00 sph 20/HM

DFE...
Post-Dilated Retinoscopy...

- OD: -4.75 -1.25 x 90  20/20
- OS: -29.00 sph  20/800

• Myopic Degeneration OS = Dx
Myopic Degeneration

- Field
- Usually > 6.00 D myopia
- Complications:
  1. Retinal breaks
  2. Choroidal neovascular membranes
     - 5-10% of cases with axial length >26.5 mm
  3. Fuchs's spots
     - Previous CNVM and/or subretinal hemorrhages
  4. Posterior staphylomas
  5. Lacquer cracks — breaks in Bruch's membrane complex; 4% eyes
  6. PVD
     - Occurs at earlier age
  7. Diffuse pigmentary alteration/chorioretinal degeneration
  8. Lattice Degeneration — not more common in myopic degeneration
  9. Increased glaucoma risk

Treatments?

- Controversial...
- Myopia control???
  - Spectacles: single vision vs. MF's
  - GP: single vision vs. MF's
  - Ortho-K
  - Atropine/Pirenzepine
- Scleral reinforcement???
- CNVM:
  - Laser photocoagulation
  - Anti-VEGF agents
Case History...

- 49 YO AAF

- CC: “doing well... just want Rx updated”
- POH: history of “dominant/familial drusen”, (-) trauma
- PMH: (+) bilateral hearing loss since birth
- FMH: unremarkable
- SH: unremarkable
- ALL: denies

Exam...

- VA = 20/20 OD, OS (cc)
- EOM's = WNL OU
- Pupils = WNL OU
- CVF = WNL OU

- Refraction:
  - OD: -1.75 – 0.75 x 090  20/20
  - OS: -1.75 – 1.25 x 060  20/20

- SLE = WNL OU; early cataracts OU
- Tonometry = 18 mmHg OU with Goldmann

DFE...
Diagnosis in the past...

• Dominant Drusen = previous diagnosis

• Differentials now...
  • Usher’s Syndrome with RP
  • Syphilitic Chorioretinopathy
  • Rubella Retinopathy

Electrophysiological & Lab Tests...

• ERG = normal

• CBC with diff = WNL
• FTA-ABS = negative
• RPR = negative/non-reactive
• Rubella IgG = positive
  • (greater than 10 = positive/immune)
  • Patient’s level was 13.8
Dx = Rubella Retinopathy...
- Togaviridae family, found only in humans
- Respiratory tract transmission
- Consequence of rubella infection in utero
  - Ocular & systemic complications possible
- Last major worldwide pandemic was 1963-65 (50 YO today)
  - 10% of all pregnant women infected, 20% of those pregnancies resulted in CRS
- Triad: heart disease, deafness, & cataracts
- 70-90% of worldwide population has antibodies to Rubella
- 95% of US population is seropositive due to vaccines
- Risk of malformations during pregnancy = first 16 weeks is largest risk
  - 10% - 1-3 weeks
  - 3% - 11-12 weeks
  - 2% - 13-16 weeks
  - 1% - 17-18 weeks
  - 0% - 19+ weeks

Immune System & Rubella...
- Non-immune maternal exposure to Rubella virus during 1st trimester of pregnancy
  - If mother has immunity, then risk is virtually nil
- Organogenesis occurs 1-8 weeks of gestation
  - Maternal IgG is only Ig that can cross placenta... however, this occurs around 8 weeks of the earliest...
    - May IgG from mother around 12 weeks gestation
    - IgG is large, never crosses placenta
    - IgG only the maternal surface... does not cross placenta
    - Endogenous IgG synthesis at 24 weeks gestation by fetus
  - An acquired infection around this time (1st trimester) can easily affect the vulnerable fetus due to “no defense”
    - Biggest risk to fetus is here
    - Most active organogenesis and most rapid cell division here

Rubella Pathogenesis...
- Reduced organogenesis:
  1. Cellular deficiency => tissue destruction/scarring
    - Decreased growth rate
    - Shortened survival time
  2. Endothelial cell damage => vascular damage
    - Notably, inflammation does not seem to play a role in pathogenesis
- Risk of CRS after re-infection is only 5-8%
Congenital Rubella Syndrome

1. Congenital cardiopathy
   - 30% of cases

2. Sensorial deafness
   - Most common
   - 60% of CRS cases

3. Ocular defects (30-43% of CRS cases)
   - Salt ‘N Pepper Retinopathy – 60% of CRS
   - Nuclear Cataracts – 27% of CRS cases; must be ≤6 weeks gestation
   - Microphthalmia – 10-20% cases
   - Iris atrophy – notoriously poor dilators; difficult phaco
   - Glaucoma (~10-15% cases)
   - Strabismus/Ambyopia
   - Hyperopia > myopia (shorter eyeballs)

Salt ‘N Pepper Retinopathy

- Pathognomonic for prenatal rubella infection
- Pigmentary retinopathy of RPE
  - Neural retina = unaffected
  - Choroid = unaffected
  - 40-60% of CRS cases
  - Non-progressive (vast majority)
  - Electroretinogram (ERG) = normal too
  - CNVM possible

FAF vs. FANG in Dx of Rubella Retinopathy...

- “...fundus autofluorescence (FAF) can sensitivity and noninvasively highlight areas of dysfunctional RPE. Thus, FAF in the absence of FANG can be sufficient to establish the diagnosis of rubella retinopathy.”
  - Goldberg N, et al. (2009)
Rubella Retinopathy Expectations

- RPE pigmented changes & hearing loss ➔ Think Rubella!
- Good vision is the rule
- ERG = normal
- Dilation can be difficult….may need multiple mydriatics…
  - Iris atrophy 2' poor development of iris dilator muscles
- When in doubt…consider IgG/IgM
  - Rule out syphilis!
- Ask about maternal infections during utero….a lot of patients are aware!

MMR Vaccine and Seropositivity

- MMR = measles, mumps, rubella
  - Given within first year of life in developed countries now
  - Repeat around 15 years old too

  "...confirmation by RT-PCR, serum rubella IgM or persistently high levels of IgG were not useful since laboratory evidence of rubella virus must be obtained in the first year of life to be informative."
  - Tamayo MT, et al. (2013)

- IgG will be persistently high in anyone who has been given the MMR vaccine in past
  - What about my patient then???

Another case of Rubella Retinopathy...52 YO AAF

- [Images of retina]
Case #10:

• “Doc, I’m having trouble reading for quite some time now.”

Case History

• 62 YO AAM
• “Blurry vision”
• HPI: OD only, onset “some time ago”, constant, gradual until it stabilized
• PMH: denies; LME unknown
• Meds: denies all
• All: NKDA
• SH: every day smoker

Exam

• BCVA: 20/40 OD, 20/20 OS
• CVF, Pupils, EOM’s = WNL OU
• Slit lamp = WNL OU
  • Some minor cataracts OU
• Tonometry = 9 mmHg OD, 10 mmHg OS
• DFE: see pics
Sent for FANG....

• Unable to complete secondary to “extravasation”
  • Missed vein...NaFl got into surrounding tissues

• Patient declined further attempts
  • Monitor only

6 weeks later...

(+): Stable appearance and vision OD

OCT is stable 6 weeks later OD

--- Elected to monitor patient x 3-6 months given stability
--- Will refer for FANG and/or Avastin injection if any changes occur.
Polypoidal Choroidal Vasculopathy

- Controversial overall...
  - Idiopathic; aka—“posterior uveal bleeding syndrome”
    - Technically classified under “ARMD”
  - Typically unilateral; M = F
  - Main differential Dx = ARMD!!!
    - Younger age of onset than ARMD
    - Persons of "color" more often; Asians > African-Americans ??
    - Only 8-13% of Caucasians with CNVM
    - Lack of drusen!
    - Characteristic FANG/ICG and OCT findings;
      - ICG is more helpful than FANG!
  - "Typically has a relapsing-remitting course with chronic, multiple, recurrent serosanguinous detachments of the RPE, neurosensory retina, and subretinal NVM."

ARMD vs. PCV

<table>
<thead>
<tr>
<th>ARMD</th>
<th>PCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older patients</td>
<td>Younger patients</td>
</tr>
<tr>
<td>Caucasians</td>
<td>Non-white races</td>
</tr>
<tr>
<td>Drusen present</td>
<td>Drusen absent</td>
</tr>
<tr>
<td>Macular location</td>
<td>Extra-macular, peripapillary</td>
</tr>
<tr>
<td>Indistinct lesions</td>
<td>Distinct lesions</td>
</tr>
<tr>
<td>Genetic background</td>
<td>Genetic background</td>
</tr>
<tr>
<td></td>
<td>Choroidal vascular hyperpermeability</td>
</tr>
</tbody>
</table>

- Although, these are different pathologies…“PCV is a type of choroidal neovascularisation. Hence, PCV is currently categorized as a phenotype of age-related macular degeneration (AMD).”
  - Honda S, et al. (2014)

PCV Associations/Risk Factors...

- Hypertension (41-45%)
- Smoking
- Elevated CRP
- h/o CSCR
- Myopic degeneration w/ staphyloma
PCV Stages...

1. Orange/Red lesion in choroid/sub-RPE layers
2. Pigment Epithelial Detachment with +/- SRF
3. Subretinal fibrinous material after resolution
   • My patient likely is in this stage

Treatment...

• Very similar to wet ARMD and dry ARMD...
  • Anti-VEGF injections
  • Photo-dynamic therapy
  • Combo: PDT & Anti-VEGF = added benefit!
  • If inactive, monitoring retina q6 months is appropriate

• "Patients found to have exudative, hemorrhagic retinopathy, without signs of active inflammation or precursors to ARMD, should be considered suspicious for IPCV."
  ---Handbook of Ocular Disease, Review of Optometry (2013)

Idiopathic Intracranial Hypertension Update

Chris Borgman, OD, FAAO
Southern College of Optometry
Memphis, TN
COPE Disclosures:

--I do not have any relevant financial relationships to disclose.

--The content and format of this course is presented without commercial bias and does not claim superiority of any commercial product or service.

Disclosures...

• I have no disclosures to report.
• I'm not perfect...
• I can email you my reference list...
• Questions??
  • Email me: cborgman@sco.edu

Case 1 --- 35 YO AAF  (20/20 sc OD, OS)
Baseline OCT

Avg RNFL:
131 µm OD
132 µm OS

Baseline HVF

--workup → IIH!

--Started on Diamox 500mg BID PO by neurology
Case 2:

“Doc these headaches are killing me!... will new glasses help?”
Case History:

"fits the profile"

- CC: "progressive loss of side vision and now central vision"
  - OD<<OD, (+) HA's behind eyes, onset 2-3 mo, referred by PCP after no improvement with oral antibiotics for "viral infection"
- BCVA = 20/25 OD, 20/1000 OS with Snellen
- Color Vision = 1/7 OD, UTT OS with HRR Plates
- CT = ortho at D & N
- EOMs = Full OU
- IOP = 16 mmHg OD, 18 mmHg OS with Goldmann
- BP= 114/73 in-office
- PMH = (+) HTN—controlled, (-) DM, (-) pregnant
- Meds = Atenolol
- Allergies = NKDA

More mag please...
FL = 8/14
FP = 4%
FN = 69%

VFI = 16%
MD = -26.60 dB
PSD = 9.92 dB

FL = 0/12
FP = 0%
FN = 7%

VFI = 38%
MD = -24.61 dB
PSD = 11.47 dB

Avg RNFL:
78 µm OD
76 µm OS

MRI results for patient
- MRI = WNL
- MRA = WNL
- MRV = bilateral stenosis of transverse sinuses
- LP opening pressure = 295 mm/H20
- LP Cytology = normal

Management? What would you do now?
Idiopathic Intracranial Hypertension (IIH)

- **AKA** Pseudotumor Cerebri (PTC) or Benign Intracranial Hypertension (BIH)
- **Defn:** increased ICP without a mass effect and with normal CSF composition
- **MOA:** intracranial venous drainage obstruction; decreased CSF drainage
- **F>>M (90% vs. 10%)**; females of child-bearing age
- **Risk factors = obesity (70% of IIH), delayed CSF absorption, venous outflow abnormalities/increased cerebral venous sinus pressure**
  - Recent estimates of IIH & obesity → 90-95% patients are obese!
- **Headaches = 90-94% of cases**
  - Most common Sx
- **Papilledema = most common Sn; 89.95% of cases**

Available theories of IIH pathophysiology...

- 1. CSF hypersecretion
  - But why no hydrocephalus/ventricular hypertrophy noted?
- 2. Reduced CSF resorption
- 3. Obesity
  - Increased intrathoracic pressure gradient → decreased venous return from brain
- 4. Hormonal
  - Women of child-bearing age are most common and affect IIH/PTC
  - No hormonal profile has been identified
- 5. Endothelial dysfunction/inflammation
  - Obesity increases both of these
- 6. Aquaporin (CNS water channel proteins) deficiencies
- 1. Acetazolamide lowers expression of aquaporin molecules...

**Bottom Line:** We don't know yet!
IIH prevalence expected to increase!

• US population is becoming more obese
• IIH cases expected to increase
• 57% IIH patients go on disability
• 31% IIH patients change jobs
due to IIH
• $444 million/year spent on IIH management in US!

Modified Dandy’s Criteria (Revised 2013)

1. Absence of mass lesion or hydrocephalus with CT or MRI
2. Elevated CSF opening pressure upon lumbar puncture with normal CSF profile
   - Non-obese patient >200 mmH2O = Abnormal
   - Obese patient >250 mmH2O = Abnormal
3. Intact neurological exam with the exception of visual disturbances, and/or 6th nerve palsy, and/or papilledema

New Updated Guidelines for IIH Dx

<table>
<thead>
<tr>
<th>Table 1: Revised diagnostic criteria for the pseudotumor cerebri syndrome in adults and children [1]</th>
</tr>
</thead>
<tbody>
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<td>1. Absence of mass lesion or hydrocephalus with CT or MRI</td>
</tr>
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<td>2. Elevated CSF opening pressure with lumbar puncture with normal CSF profile</td>
</tr>
<tr>
<td>- Adult patient &gt;250 mmH2O = Abnormal</td>
</tr>
<tr>
<td>- Pediatric patient &gt;280 mmH2O = Abnormal</td>
</tr>
<tr>
<td>3. Intact neurological exam with the exceptions of visual disturbances, and/or 6th nerve palsy, and/or papilledema</td>
</tr>
</tbody>
</table>

References:
### PTC/IIH Symptoms

1. **Headache** (worse upon awakening) *(84-94%)*
2. Transient Vision Loss *(62-68%)*
   - Unilateral and/or bilateral possible
3. Pulsatile Tinnitus *(48-52%)*
4. Blurred Vision
   - Severe vision loss *(25%)*
   - Blindness *(10%)*
5. Vomiting
6. Diplopia *(18%)*

---

### PTC/IIH signs...

- **Papilledema!** In *up 95%* of cases! *(Puffer et al. 2014)*
  - “With rare exception, all PTC/IIH patients have papilledema, a hallmark of subacute intracranial hypertension.” — Galgano et al. *(2013)*
  - But...
  - Although papilledema is present in the vast majority of PTC/IIH patients, its absence is not an exclusionary criteria.” — Galgano et al. *(2013)*

---

### Ocular work-up in IIH...

- Visual Acuity
- Visual Fields
- EOM's
- Fundus Exam
- Retinal Imaging *(FP, OCT, etc.)*
- Color Vision
- Contrast Sensitivity

Most important to assess in IIH
Visual Acuity and Color Vision in IIH

- **Visual Acuity**:
  - Acuity tests foveal function
  - Not typically affected unless edema extends into central 10° of fixation

- **Color Vision**:
  - Only been found to be abnormal in ~20% of cases
  - Ishihara defects only noted in the existence of moderate to marked visual loss and optic atrophy
  - Not the most reliable way to follow patients

EOM’s/VF’s in IIH...

- **EOM’s**:
  - If present, uni/bilateral 6th nerve palsies are present 2° stretching nerve between apex of clivus bone/Dorello’s canal and exit zone of 6th nerve on brainstem
  - Dilation required in all 6th nerve palsies to rule out/in papilledema per Will’s Eye Manual

- **Visual Fields**:
  - *Most important test to follow for changes*
  - Enlarged blindspot first to show, followed by generalized constriction, and nasal defects.
  - Any kind of defect is possible though...

VF’s in neuro-optometry.... Is testing the central 30° enough?

- "Humphrey SAP has replaced Goldmann perimetry in clinical practice despite fears that peripheral visual field defects may be missed. This fear seems unwarranted as only 1-2% of patients with nonglaucomatous VF defects have abnormalities in the peripheral field beyond 30° degrees in the absence of central field defect."

- Alternatively said....98-99% of neurological VF defects will show up in the central 30° when tested... pretty good odds!
Neuroimaging/workup in IIH...Order is important...why???

1. Order MRI/MRV first
2. Followed by lumbar puncture if MRI/MRV is normal
   - >250 mmH2O in adult patients = abnormal
   - >280 mmH2O in pediatric patients = abnormal

   Herniation through foramen magnum can compress upper medulla which is where the respiratory and cardiovascular centers are located → Death


What are we looking for in work up?

- MRI
  - Rules out space occupying mass, hemorrhage, etc.
  - Empty sella, pituitary deformities, distention of ON, posterior globe flattening
- MRV
  - Rules out transverse sinus stenosis and/or venous sinus thrombosis
- Lumbar Puncture (LP)
  - Document elevated opening/intracranial pressure
- LP cytology and culture
  - Rule out infectious meningitis, blood, and other possible issues/causes

Question I’ve received from previous CE attendees:

- Is LP required in a patient with normal MRI/MRV and papilledema?
  - "Lumbar puncture to measure opening pressure and spinal fluid examination are critical for the diagnosis." – Peralta, et al. Curr Opin Ophthalmol. 2018
  - "Despite the value of neuroimaging in the diagnostic workup of IIH, it does not replace the need for measurement of lumbar opening pressure as imaging abnormalities show a wide interindividual variation and none of the findings are pathognomonic of IIH… LP is mandatory in the diagnostic algorithm of IIH." – Hoffmann, et al. J Headache Pain. 2018
  - "Following normal imaging, all patients with papilledema should have a lumbar puncture to check opening pressure and ensure content is normal." – Mollan, et al. J Neurol Neurosurg Psychiatry. 2018
CSF Hydrodynamics

- Oh crap.....you’re kidding me right?
  - Nope, not kidding...

Where is CSF made again???

Answer: Choroid Plexus in Lateral, 3rd, & 4th Ventricles

Where does CSF drain to?

- CSF is absorbed from the subarachnoid space across the arachnoid villi into the venous circulation.
- The arachnoid villi act as one-way valves between the subarachnoid space and the dural venous sinuses. The rate of absorption correlates with the CSF pressure.
  - "Pressure gradient valves"
- Dural Venous Sinus Thrombosis important to rule out with MRV!
Pathophysiology of IIH...

- Any blockage along this CSF drainage pathway or in the venous sinus drainage can result in increased ICP!
- Bottom Line MOA = obstruction of intracranial venous drainage

PTC /IIH Treatment Options...

1. Weight loss (5-10% is sometimes curative)
2. Carbonic anhydrase inhibitors (6-50% less CSF production)
   - Acetazolamide and/or Topiramate
   - No oral steroids → weight gain
3. Ventriculoperitoneal Shunt / Lumboperitoneal Shunt
   - Headaches only; vision stable
4. Optic Nerve Fenestration
   - Vision/Visual Field worsening; no headaches
5. Venous Sinus Stenting
   - In venous sinus stenosis

Topamax vs. Diamox?

- **Acetazolamide**: CAI inhibitor; works on ciliary body and choroid plexuses
  - It has been shown to reduce CSF production in humans by 6% to 50%. This inhibition appears to require a higher dosage than is routinely used (routine dose: 1 g/day po)
  - Average weight loss of 7.7% was obtained in one year on medication

- **Topiramate**: novel anticonvulsant with many MOA; epilepsy/migraines
  - Sulfonamide drug...be careful of sulfa allergies
  - Also has carbonic anhydrase inhibition component; and decreases appetite
    - Weight loss of 5-10% alone may be curative in some cases of IIH
    - Average weight loss of 7.7% was obtained in one year on medication
  - Monitor for angle closure glaucoma and myopic shift!!!
    - 85% of this happens within first 2 weeks of therapy
    - Ciliochoroidal infi
      - **SIs**: rise in intracranial pressure causing forward displacement of the lens-iris diaphragm with resultant narrowing of the anterior chamber
      - SDs: med. cyclopentolate and OIP lowering meds may be needed. LPI not helpful.

References

How long should CAI’s be maintained?

- Can/Should Tx ever be discontinued once Sn/Sx are under control?
- A long-term follow-up study was done in PTC patients using a CAI (acetazolamide) over 6.2 years.
- 54 total patients followed for over 6 years
- 60% of patients experienced multiple recurrent episodes over this time span
- None of the recurrences occurred while maintained on acetazolamide!
- Good evidence to maintain long-term Tx???


Idiopathic Intracranial Hypertension Treatment Trial (IIHTT)

Effect of Acetazolamide on Visual Function in Patients With Idiopathic Intracranial Hypertension and Mild Visual Loss: The Idiopathic Intracranial Hypertension Treatment Trial

What was being investigated?

- To determine whether acetazolamide is beneficial in improving vision when added to low-sodium weight diet in patients with IIH and mild vision loss over a 6 month period of Tx
- N=165 (86=acetazolamide & diet, 79=placebo & diet)
  - Completed: n=126 (69 vs. 57)
  - 2 to -7 dB perimetric mean deviation at baseline
  - Acetazolamide initial dosage = 500 mg BID PO
  - Increase in 250 mg tablet every week up to 4000 mg/day!!!
Outcomes being measured...

- Primary outcome = change in PMD from baseline → 6 mo in most severe eye
- Secondary outcomes
  - change in PMD from baseline → 6 mo for better eye
  - papilledema grade
  - CSF pressure
  - visual acuity
  - QOL
  - vital signs
  - lab results
  - presence of HA
  - treatment failure

Visual Field Findings...

- Acetazolamide/Diet = 1.43 dB improvement
- Placebo/Diet = 0.71 dB improvement
- Acetazolamide/Diet = 0.87 dB improvement
- Placebo/Diet = 0.42 dB improvement

Papilledema Grading...

- Papilledema grade 3.5 = 2.27 dB improvement
- Papilledema grade 1.2 = -0.67 dB improvement

- Significant improvement in acetazolamide groups in study and fellow eyes with FP's
- QOL improved too
- Weight change
  - -3.50 kg in acetazolamide at 6 mo
  - -3.45 kg on placebo at 6 mo
- CSF Pressure
  - -102.5 mmH2O on acetazolamide at 6 mo
  - -52.4 mmH2O on placebo at 6 mo
- No change in headache severity or visual acuity
  - 69% still had headaches on acetazolamide at 6 mo
  - 68% still had headaches on placebo at 6 mo
Adverse Events

- 9 total patients in study dropped out
- Decreased CO2 levels
- Increased Cl- levels
- Mild decrease in potassium levels (no supplementation needed)
- No changes to sodium
- No liver function changes

**Conclusion:**

"In patients with IIH and mild visual loss, the use of acetazolamide with a low-sodium weight-reduction diet, compared with diet alone, resulted in modest improvement in visual field function. The clinical importance of this improvement remains to be determined."

---

1. Monitor K levels?

- No participant on acetazolamide alone required potassium supplementation; thus, routine monitoring of potassium levels is not recommended.

2. Monitor with CBC with differential?

- No patient experienced aplastic anemia and periodic monitoring of blood cell counts is not necessary or cost-effective.

Allergy to acetazolamide?

- "Allergic reactions to acetazolamide were uncommon. Furthermore, there is no evidence to suggest that an allergy to sulfonamide antibiotics increases the risk of an allergic reaction."
Pregnancy Considerations...

- **Topamax** = FDA Category D; evidence shows up to 10-20% of dose can be found in infants who are nursing

- **Acetazolamide** = FDA Category C; case reports of placenta crossing; has been avoided in pregnancy in the past...new evidence to suggest otherwise?

- If both are avoided in pregnancy, then sometimes repeat LP’s may be necessary in short term to keep ICP down; inherent risks...

---


National Collaborative Perinatal Project (NCPP) 1959-1974

- “The use of carbonic anhydrase inhibitors (CAIs) has a large pool of human data on which to base clinical decisions. The source is the National Collaborative Perinatal Project (NCPP) conducted by the NIH from 1959 through 1974. This study monitored more than 50,000 mother-child pairs and 1,024 instances of systemic usage of acetazolamide during pregnancy. In the resulting offspring, there were 18 instances of malformations. The predicted number due to chance was 18.06. This suggests that the incidence of malformations from acetazolamide exposure during pregnancy is no greater than the natural incidence. In the same study, there were 12 documented first trimester exposures to acetazolamide. No anomalies were observed in the resulting offspring.”

---

Steven Odrich, MD (Bronx, NY)

http://www.aao.org/publications/eyenet/200906/letters.cfm?RenderForPrint=1&


- 12 patients on Diamox 500 mg BID PO during pregnancy
- No adverse side effects nor congenital malformations noted
- Cited the results of the Collaborative Perinatal Project as well

- “In summary, there is no convincing evidence from the literature for the recommendation to limit the use of acetazolamide for IIH in pregnancy. Although the use of acetazolamide might be restricted in the first trimester, this recommendation may have a more medicolegal than medical rationale. It is our recommendation that acetazolamide be considered if the risk of nontreatment (e.g., progressive visual loss) is sufficiently high to warrant its use.”

• “There is clearly a lack of convincing evidence for a teratogenic effect associated with this use of acetazolamide during pregnancy. In all reported cases, there is no common morphological abnormality that one would expect with a teratogenic agent, and specifically, there are no cases of postaxial limb malformations in human offspring as found in animal models.”

• “In summary, our study confirms the lack of convincing evidence for adverse effects of acetazolamide use in human pregnancy, even when prescribed prior to the 13th week of gestation. We agree with Lee et al that the avoidance of acetazolamide during the first trimester has very little medical justification and is mainly guided by medical-legal rationale.”

---

Question to y’all:

Is it appropriate for O.D.’s to prescribe Diamox for these patients long term???

---

Surgical Considerations...

1. Headaches only, vision stable (can be used for both HA’s and vision too)  
   ----- LP shunt, VP shunt
2. Vision loss/VF worsening despite maximal medical Ts  
   ----- Optic Nerve Fenestration
3. Venous sinus thrombosis  
   ----- Anticoagulants
4. Venous sinus stenosis  
   ----- Venous sinus stenting

* Majority can be managed via weight loss and oral meds (Diamox)
1A) Ventriculo-Peritoneal Shunts (VPS) and Ventriculo-Atrial Shunts (VAS) in IIH

1B) Lumboperitoneal shunts in IIH

- L3/L4 or L4/L5 spaces most commonly used
- Drain into peritoneal space like VPS

VPS vs. LPS...

- Ventriculo-Peritoneal Shunt (VPS):
  - Infection rate of 7-15%
  - 20% revision rate q2 yrs

- Lumbar Peritoneal Shunt (LPS):
  - Infection rate of 1%
  - 50% revision rate q2 years

- "In short, most shunted PTC patients require multiple revision surgeries during their lifetime."
  — Galgano MA et al. (2013)
2) ON Sheath Fenestration...
- Described in 1872 by DeWecker; expanded upon by Heyreh in 1964
- **Defn:** make slits in ON sheath to reduce the local pressure around the optic nerves.
- ~50% of unilateral ON sheath fenestration procedures results in resolution of visual symptoms in both eyes.
  - Both optic nerves are connected via the subarachnoid tissue around the optic chiasm
- Typically only done for visual Sn/Sx without headaches...
  - If headaches \(\rightarrow\) shunt procedure may be better option
- Safe and effective up to 10 years per several studies
- Revision rate is usually very low; 1 procedure per lifetime generally

---

**Optic Nerve Fenestration**
- ONSF procedure is approximately 25-30 minutes in duration for a bilateral operation
  - (10-15 minutes per eye)

---

**Super hard question to answer:**
---When should I send for ONSF ??
- "At present, evidence-based guidelines for when ONSF should be utilized in the management of vision loss in IIH do not exist."
- "Neither are there any prospective studies to guide surgical decision making, nor are there data comparing ONSF visual outcomes to CSF diversion or medical therapy."
- "When visual loss is noted at presentation, Corbett et al have recommended consideration of ONSF early in the clinical course. Banta and Farris recommend ONSF when progressive visual loss, as defined by loss of >2 lines of Snellen acuity or new onset or progression of VF defect, occurs despite initial medical management."
Define “Progression of VF defect” please!?

• In IIHTT by NORDIC Group → MD of < -7.00dB used for surgical cutoff

• Treatment failure of Acetazolamide defined in NORDIC1
  • Baseline MD of: 0.00 to -3.5 dB >worsened by >2 dB
  • Baseline MD of: -3.5 to -7.0 dB >worsened by >3 dB

{ Confirmed twice by repeat VF’s. }


Criteria for ONSF by OSU in Columbus, OH

• Indications for ONSF included persistent symptomatology (i.e., headache) and/or signs (i.e., papilledema) associated with increased intracranial pressure despite maximal medical therapy or neurosurgical shunting, or severe vision loss at presentation.

• ONSF procedure is approximately 25-30 minutes in duration for a bilateral operation (10-15 minutes per eye)


How often is ONSF actually needed for IIH?

• Only 14 patients (31 eyes) over a 7-year period actually needed ONSF in a tertiary referral center…

• Shows how uncommon the need for ONSF really is!

New Study!
Surgical IIH Treatment Trial (SIGHT)

- Currently underway and recruiting!
  - Starting date → October 2018
  - Estimated completion date → June 2021
- Randomized clinical trial
- n=180 patients

- Compare the following surgical options in IIH patients:
  1. Medical therapy alone (ie Diamox and diet/weight loss)
  2. MT + ONSF
  3. MT + VP shunting

https://www.clinicaltrials.gov/ct2/show/NCT03501966

3) Dural Venous Sinus Thrombosis

- Blood clots in young people are not normal...
- If DVST occurs, hematological workup and anticoagulant therapy is required.
  ---Subramanian PS et al. (2014)
- Consider: CBC with diff, CMP, lipid panel, PT/PTT, Protein S, Protein C, Homocysteine levels, Lupus anticoagulant, anti-cardiolipin, Factor V Leiden, Prothrombin mutation, Antithrombin III mutation, Sickledex screen, Hemoglobin electrophoresis
DVS Thrombosis Treatment...

- Rule out clotting disorder, infection, etc.
- Aggressive anti-coagulation (heparin, warfarin, clopidogrel)
- Not a candidate for DVS Stenting in vast majority of cases...
- If anticoagulation and oral CAI's do not work, then may need shunt surgery

Dural Venous Sinus Stenosis

Dural Venous Sinus Stenosis (DVSS)

- **Defn**: focal, narrowed section of dural venous sinuses causing back up/turbulent venous blood flow
- *Most common at junction of Sigmoid and Transverse sinuses
- Not a true blood clot like DVST is...
- Treatment = weight loss, oral CAI, and/or DVS Stenting procedure
DVSS in IIH vs. Normals...

- Focal stenosis has been demonstrated in 90% of IIH patients using advanced imaging techniques.
- Furthermore, focal stenosis in the same sinus territory was only demonstrated in 6.8% of asymptomatic control subjects.
- Might be on to something here....

4) Dural Venous Sinus Stenting

- Right transverse sinus is dominant in 73% of cases
- MOA: Increases drainage of venous blood from venous sinus system which helps with the pressure dependent valves, arachnoid villi granulations, allowing them to clear CSF in to the venous system more efficiently/quickly → decreasing ICP
- High frequency of resolved or improved HA's and papilledema with this method

DVS Stenting...

- Not every patient is a candidate for DVS Stenting
- Criteria Needed:
  1. Presence of venous sinus stenosis (MRI/MRV); not thrombosis...
  2. Transvenous manometry across the stenosis >10 mmHg differential
- Catheter with stent and manometer placed in femoral vein and "fished" upwards to location of sinus stenosis
- Post-Op Medications:
  - Plavix 75 mg x 6-12 weeks then d/c
  - ASA 325 mg for life
Dural Venous Sinus Stenting for IIH

Suboccipital/Subtemporal Cranial Decompression

- Very invasive; but historically pretty successful...
- Remove part of skull to allow for more room inside...
- Not gold standard anymore
- Can be used in severely refractory cases unresponsive to traditional surgical procedures for ICP and IIH

Optometry IIH/PTC Summary...

- Make the diagnosis
- Get MRI/MRV
- Refer for LP
- Neurology should start Diamox/Topamax

- Monitor x 1 month post med Tx, then q3-4 months until resolution/stability (varies)
- Serial OCT, FP, and HVF's are necessary to gauge Tx/stability
- Relay findings to managing neurologist/PCP regularly
- Encourage weight loss
What happened to patient #2?

- "No-showed" to neurologist twice!
- Has not returned phone calls or letters...
  - Phone has been disconnected...
- Possible candidate for ONSF? DVSS? Diamox only? All 3?
- "You cannot care more for a patient than what they care for themselves." — Joseph Sowka, OD and Alan Kabat, OD

Questions???

- Thanks!!
- Email: cborgman@sco.edu

Glaucoma:
What would you do?

Chris Borgman, OD, FAAO
Memphis, TN
COPE Disclosures:

--I do not have any relevant financial relationships to disclose.
--The content and format of this course is presented without commercial bias and does not claim superiority of any commercial product or service.

Disclaimers...

• I have no financial disclosures to report!
• Reference list available!
• I’m obsessed with Sasquatch!
• Email me: cborgman@sco.edu

Ground Rules...

• Don’t look ahead!
• This lecture is based on questions I’ve personally had “in the trenches” of patient care...
• I don’t have all the answers...
• I’m not perfect...
• There are perks with working at SCO with 60+ doctors...
• It’s OK to disagree somewhat in glaucoma diagnoses...

“Even with the same available data, one doctor’s interpretation of the results [with subsequent initiation of therapy]—or not—may vary tremendously from the approach of another clinician....Equally competent doctors have different thresholds and different philosophies.”

Metcalf & Thomas, Ophthalmic Drug Guide 2017
Case #1

Case History...

- 63 YO AAF
- (+)HTN → BP in-office: 136/83
- Meds: amlodipine & benazepril
- BCVA: 20/20 OD, 20/20 OS
- IOP: 28 OD, 30 OS with Goldman
- Gonio: WNL OU

DFE...
Do these VF defects correlate with optic nerve appearance?
Management...

• Started Latanoprost qhs OU.......RTC 1 month

• 1 month later:
  • IOP: 26 OD, 28 OS via Goldman
  • iCare: 21 OD, 25 OS

But was 28 OD, 30 OS truly the maximum IOP? Low? High? Average?

What is definition of “non-responder”? 

• Varies per source!
• **Most commonly used:
  • ≤10% reduction in IOP from baseline over 1-2 visits
• Other studies have used:
  • <20% IOP reduction from baseline
  • <5 mmHg IOP reduction from baseline

How often are patients “non-responders” to PGA meds?

• Non-response rate of latanoprost → up to 28% in some studies!
• Other studies show 18-25% non-response rate with PGA’s
• Bottom Line: ~20% failure rate overall
Do all PGA's lower IOP equally?

- Premise: Lumigan vs. Travatan vs. Xalatan in Tx-naïve patients; is one better?
- N=122 patients...OHTN, POAG, PEX, PDG
- Completely independent study → no pharm companies involved/sponsored
- 40 bimatoprost, 42 latanoprost, 40 travoprost
- Followed for 6 months:
  - Bimatoprost = 35% reduction IOP
  - Latanoprost = 29% reduction IOP
  - Travoprost = 30% reduction IOP
- Differences were NOT statistically significant!
- “All the three drops are well-tolerated; and the difference between their tolerance and efficacy at 6 months was similar. These results may reassure ophthalmic departments when choosing a first-line prostaglandin analogue when managing patients with glaucoma or ocular hypertension.” — Faridi, et al. 2010.

- Premise: meta-analysis looking at all 4 PGA meds; which one is best?
- N=4834 patients on PGA meds, 1731 patients on timolol
  - 1247 pts = bimatoprost
  - 1721 pts = latanoprost
  - 1207 pts = travoprost
  - 659 pts = tafluprost
- All reached 30% IOP reduction target better than timolol; equally among PGA's
- “By applying an advanced technique known as network meta-analysis that compared all 4 PGAs simultaneously, we showed that bimatoprost 0.03% had greater efficacy in achieving the outcome of proportion of patients reaching target IOP reduction of at least 30% from baseline, followed by travoprost 0.004%=latanoprost 0.005%, and tafluprost 0.0015%.”
- Bottom Line for Overall IOP reduction:
  - All work well for 30% reduction in IOP
  - Bimatoprost > travoprost > latanoprost > tafluprost


If one PGA fails, switch to another PGA?
Switching between PGA’s?

<table>
<thead>
<tr>
<th>Latanoprost</th>
<th>→</th>
<th>Lumigan</th>
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<th>Travatan</th>
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<th>Zioptan</th>
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Back to case...

- Switched to Lumigan qhs OU
- IOP 1 month later... 20 OD, 20 OS
- Did I give latanoprost enough time?
- How/why does Lumigan work better?

How/why is bimatoprost different?

- “Bimatoprost is unique, in that it also has an effect on the conventional pathway. Thus, bimatoprost has a dual mechanism of action, whereby it lowers IOP by acting on both the pressure-sensitive and -insensitive outflow pathways.”

- N = 30 patients; latanoprost → bimatoprost
- “Following the switch to bimatoprost, the additional percent of IOP lowering ranged from 17.8 to 22.0% in OD and from 15.0 to 24.0% in OS. Of note, no further adjunctive IOP lowering therapy was added to the regimen of any patient after the switch to bimatoprost.”

PGA’s in general:  What do I do?

• My general trend:
  - Start with generic latanoprost due to $$$$$
  - RTC 4-6 weeks
  - If less than expected IOP reduction occurs….reinforce compliance
  - RTC 2-3 months later
  - If IOP still less than expected, switch to bimatoprost
  - RTC 4-6 weeks
  - If minimal (or no response) I may add adjunctive med to PGA, or abandon PGA's altogether
  - If patient fails 2 different PGA's, then I typically abandon PGA class
    • But this is super rare!

When is best time for PGA administration?

• N = 30 ; QPM x 1 month then switch to QAM x 1 month

• "There was no statistically significant difference in IOP response to the medication between morning and evening dosing. This may represent a potentially greater effect of the medication dosed in the evening being counterbalanced by greater adherence to the medication in the morning. Although this was not a primary endpoint of this study and time of day of IOP measurement was not controlled, this is an important finding."  

• "This study shows that taking a daily topical antihypertensive medication in the morning is felt to be more convenient than the evening in this cohort of patients, which potentially could lead to greater adherence in the morning than in the evening. The convenience of morning administration may be due to a more regular morning routine for patients, difficulty remembering to instill the drop in the evening, or both."
Case #2:

Case history

- 65 YO WF
- CC: "blurry vision"
- HPI: OD=OS, slowly worsening x 6 months, (-)pain, (+)glare when driving at night
- POH: (+)POAG OU --- controlled with Travatan Z qhs OU x 5 years
- PMH: (+)T2DM, (+)HTN, (+)SLE
- Meds: metformin, lisinopril, HCTZ, prednisone 10 mg
- Allergies: NKDA
- SH: quit smoking 25 years ago, (-)EtOH

Exam...

- VA: 20/40 OD, 20/50 OS, PHNI OU
- Pupils: PERRL, (-)JAPD
- EOM's: Full OU
- CVF: FTFC OU
- MR: OD 2.00 = 1.00 x 180 20/40
- OS -2.50 sph 20/50
- SLE: 2-3+ PSC OU, 1+ cortical cataracts
- IOP: 20 mmHg OD, 19 mm Hg OS
  - Tmax: 29 mmHg OD, 28 mmHg OS
- DFE: 0.6/0.6 OD, 0.7/0.7 OS, inferior sloping OU, WNL otherwise OU
Who wants to stop the PGA prior to phaco surgery?

PGA’s and risk of CME...

- **Thought**: PGA use increases CME risk 2’ increased vascular incompetence from proinflammatory actions

- Hernstadt et al. 2017 → meta-analysis on this topic
  - 13 studies with 86,300+ eyes → 4416 on PGAs
    - 97 (out of 4416) → clinically significant CME → 2.2%
    - 28 (out of 4416) → angiographic CME → <1%

- "Based on current literature, no evidence supports stopping PGA use prior or during the course of cataract surgery to reduce CME." → Hernstadt et al. 2017

- "Apart from stopping use of PGA, reasonable alternatives include the concurrent use of NSAIDs with PGA...or to closely follow these patients for the development of CME." → Hernstadt et al. 2017


NSAIDs & PGAs: Friend or Foe?

- Does concurrent use cancel effect of each drug?
PGA's and NSAID's...friend or foe?

  - N=32; ketorolac and latanoprost
  - Ketorolac enhanced IOP lowering effect

  - N=22; diclofenac and latanoprost
  - Diclofenac may interfere with IOP lowering effect (average ~2 mmHg)

  - N=30; latanoprost and 3 PGA's tested
  - Ketorolac enhances IOP effect with PGA's

  - N=35; nepafenac and 3 PGA's tested
  - No clinical significance on IOP measurements; might potentiate IOP effect

  - N=28; bromfenac and travaprost tested
  - Bromfenac did not affect IOP lowering effect

Quick summary:
4 of 5 studies (n=125) -- Yes, use them together!
1 of 5 studies (n=22) -- No, mild effect on IOP

NSAIDs & PGAs:
Friend or Foe?

- PGA’s bind to PGF2α receptor
- NSAID’s block PG synthesis
  - No effect on PG receptors!

- Therefore, they likely do NOT interfere with one another
  - Might even enhance the IOP lowering effect

- OK to use PGA & NSAID concurrently!

Best adjunct med after PGA med???
N=52 total eyes
Purpose: After travoprost, what is best adjunct med?
IOP after one month of adjunctive treatment:
- Timolol 0.5% BID = 3.9 mmHg further IOP reduction
- Brinzolamide 1% BID = 4.0 mmHg further IOP reduction
- Brimonidine 0.2% BID = 2.3 mmHg further IOP reduction

BB vs. AA vs. CAI vs. others...
- Systematic Review and Meta-Analysis in 2010
- What is best to add to PGA?
- All agents revealed statistically similar IOP lowering efficacy:
  - 2.3 to 3.0 mmHg
- However, CAI and BB were more effective than AA
- But...
  - Neuroprotection component? → AA is best
  - Nocturnal reduction in IOP? → CAI is best

Combination Glaucoma Meds:
Review...and something new???
Cosopt vs. timolol/dorzolamide

- Cosopt > timolol alone
- Cosopt > dorzolamide alone
- Cosopt = 25-30% reduction in IOP on average
- Cosopt = timolol + dorzolamide concomitant
  - 97% confidence that they are equal treatments (Strohmaier, et al. 1998)
  - 15-20% reduction IOP for both sides
  - 0.75 mmHg more in concomitant group, significant?
- When switched from concomitant T/D → Cosopt...
  - >80% maintained IOP or had lower IOP than T/D concomitantly...
- SE’s: Cosopt = timolol + dorzolamide concomitant

Bottom Line: Cosopt = good drug!

Cosopt 3x/day instead of 2x/day???

- N = 29 patients
- BID x 4 weeks, then TID x 4 weeks
- IOP decrease:
  - BID → ~26%
  - TID → ~37%
- “Our results indicate that increasing Cosopt dosage from twice to three times a day is associated with increased efficacy in IOP reduction, with no change in its safety profile. The additional reduction in IOP was considerable and statistically significant.”


Combigan vs. brimonidine/timolol

- Combigan > brimonidine alone
- Combigan > timolol alone
- Combigan = timolol + brimonidine concomitant
  - <0.97 mmHg between groups at all study points
- SE’s: Combigan = timolol + brimonidine concomitant

Bottom Line: Combigan = good drug!
Combigan 2x/day vs. 3x/day???

- N = 31 patients
- BID x 4 weeks, then TID x 4 weeks
- IOP decrease
  - BID → ~26%
  - TID → ~36%

"The findings of this study are clinically important, because increasing the Combigan dosage achieved a statistically significant additional reduction in IOP, with no change in the safety profile."


Cosopt vs. Combigan???

- Cosopt = Combigan (Arcieri 2007)
- Cosopt = Combigan (Hatanaka M, et al. 2008)
- Cosopt < Combigan (Garcia-Feijoo, et al. 2010)
  - Only by 0.95 mmHg though!

"In this present meta-analysis, we reviewed 7 RCTs comparing the FCBT (fixed combination brimonidine/timolol) with the FCDT (fixed combination dorzolamide/timolol) in patients with elevated IOP, and found no significant difference regarding efficacy in lowering IOP at peak and diurnal mean."

- Budengeri P, et al. 2013 - meta-analysis

Final thoughts: Cosopt = Combigan!!!


Simbrinza vs. brimonidine/brinzolamide

- Simbrinza > brimonidine alone
  - Simbrinza lowered IOP by 1.0–3.0 mmHg more than brimonidine
- Simbrinza > brinzolamide alone
  - Simbrinza lowered IOP by 1.0–2.5 mmHg more than brinzolamide
- Simbrinza = brimonidine + brinzolamide concomitantly???
  - No studies on this have been published yet...

Bottom Line: Simbrinza = good drug!

FDA new drug application results: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204251Orig1s000StatR.pdf
Cosopt vs. Simbrinza??

- N=44
- Group A = Cosopt BID
- Group B = Simbrinza BID

- Morning IOP: Simbrinza > Cosopt
  - Only by 1.2 mmHg though!
- Afternoon IOP: Simbrinza = Cosopt
- SE’s: Cosopt = Simbrinza

- Bottom Line: Simbrinza = Cosopt


Bottom Line: Combination drops...

- **Efficacy:**
  - Cosopt = Combigan = Simbrinza (-ish)
  - Cost, SE’s, availability drive choice...

My general approach...

- After PGA treatment...
- Add combination med
- Then decision for SLT or incisional surgery is simpler...

- Combination meds are prescribed ~47% time as second line agent...


Compliance with drops

- Actual compliance rates = 41–72% (Kass et al. 1986)
  - 97% patients report good compliance though!
- Compliance drops from: 70% (1 med) to 50% (2 meds)
  - Greenberg 1984

Patients are lying to us!

Case #3

Case History

- 87 AAF
- POH: (+)POAG OU, Travatan qhs OU + Cosopt BID OU
- PMH: (+)HTN
- Meds: valsartan, ASA 81 mg
- Allergies: NKDA, seasonal
- BCVA: 20/30 OD, 20/30 OS
- SLE: (+)DES OU, (+)PCIOLOU, (-)PCO
- IDP: 18 mmHg OD, 18 mmHg OS
- Tmax: 20 OD, 18 OS??
Life expectancy in US in 2014...

- Per CDC:
  - Men: 76.5 yo
  - Women: 81.3 yo

What are the chances this patient makes 100 yo?

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Male Total Chance of Survival in Tennessee</th>
<th>Female Total Chance of Survival in Tennessee</th>
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<tr>
<td>80</td>
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<tr>
<td>95</td>
<td>3%</td>
<td>12%</td>
</tr>
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<td>100</td>
<td>0.7%</td>
<td>4%</td>
</tr>
<tr>
<td>105</td>
<td>0.07%</td>
<td>0.9%</td>
</tr>
</tbody>
</table>
**Heat Check:**
What are the thinnest pachs you’ve ever seen (that wasn’t keratoconus)?

![Image](428 µm and 429 µm)

**Heat Check:**
What are the thickest pach’s you’ve ever seen (without disease?)

![Image](679 µm and 670 µm)

**Is CCT ultrasound = AS-OCT???**

  - N=80 eyes
  - AS-OCT measures were thinner than UP → ~12.0 microns

  - N=240 eyes
  - AS-OCT measures were thinner than UP
    - OD: ~16.0 microns
    - OS: ~16.5 microns

**Bottom Line:** AS-OCT measures 12.0 – 16.0 microns thinner than ultrasound pachymeters!!
How do different OCT’s compare to ultrasound pachymetry???

• Brown L, Christensen M, Borgman C. The comparison of central corneal thickness amongst 4 different technology devices. AOA 2016 Poster. Boston, MA.

• General summary:
  • All 4 work great for CCT and correlate well
  • But in regards to repeatability/consistency: RTVue > Cirrus > Konan > Ultrasound

Heat Check:
What IOP is too high to just monitor?

What is likelihood of developing POAG based on IOP alone?

• OHTS = Pachy <555 and IOP 26+ = 36% (highest risk group)

• >21 mmHg = 5%
• >24 mmHg = 10%
• >27 mmHg = 50%
• >39 mmHg = 90%

• High risk of losing function if no intervention: >30 mmHg

Timeframe to advanced glaucoma?

- **Defn:** absolute scotoma within 5 degrees of fixation
- Estimated average time from earliest glaucoma VF defect/loss → advanced glaucoma
  - IOP 21-25 mmHg → 14.4 years
  - IOP 25-30 mmHg → 6.5 years
  - IOP > 30 mmHg → 2.9 years


Is there an IOP threshold that should be treated regardless if there is evidence of glaucoma damage?

- >27 mm Hg = 50% (Spaeth)
- 30 mm Hg = Chaglasian and Harthan
- 26 mmHg = OHTS study had highest risk with thin pachymetry (36%)
- 32 mmHg = OHTS maximum allowed untreated IOP

**Note:** I tend to use ~28 mmHg as my personal cut-off; but I still try to individualize Tx

**My General Rule of Thumb:** 26-30 mmHg is a reasonable cutoff in my opinion

Case #5
Case History

- 71 YO AAF
- CC: "6 month glaucoma followup"
- HPI: OS>OD, 2+ yrs, good compliance, vision stable OD, slowly worsening vision OS (?)
- POH: (+)POAG OU – latanoprost qhs OU
- PMH: (+)DM, (+)HTN, (+)hypercholesterolemia, (+)h/o breast cancer
- Meds: Lantus, Glyburide, Simvastatin, Atenolol, Valsartan
- Allergies: NKDA
- SH: unremarkable

Exam

- BCVA: 20/20 OD, 20/20-2 OS
- CVF: FTFC OU
- Pupils: PERRL, (+)APD OS with BIO light source
- EOM: Full OU
- Color: passed OU
- SLE: moderate cataracts OU
- DFE: see pics
- IOP: 15 mmHg OD, 16 mmHg OS (on latanoprost)
- Tmax: 16 mmHg OU
What is the first thing you should look at on any diagnostic test?

A. Date of exam
B. Test reliability/quality
C. Results/findings of test
D. Patient name
E. Date of birth

Pachymetry

494 µm

483 µm
Ordered CT of orbits/chiasm

- CT report:
  - "The cavernous portion of the internal carotid artery on both left and right are somewhat ectatic with atherosclerotic calcifications present, and the distal ICA on the left bulges superanteriorly toward the left optic nerve anterior to the junction of the optic chiasm, greater than on the right... Pituitary normal in size and pituitary stalk lies in the midline. Optic nerves, optic chiasm, and ICA's may be further evaluated with MRI of the brain and orbits with and without enhancement, with MRA of the brain to further evaluate carotid arteries also."
Dx = Dolichoectasia!

- Dolichoectasia = pathological enlargement of the intracranial arteries
  - Dilation, elongation, tortuosity
  - Distended and enlarged
  - Prevalence ~0.05%
  - Most commonly involves:
    - Vertebral and basilar arteries
  - Ischemia, hemorrhage, compression, & death are possible!

Dolichoectasia

- MDA: arteriosclerosis → breakdown of internal elastic membrane of artery
  - Poorly understood though...
- Associated with HTN!
- Compression of adjacent structures and/or ischemia possible
  - Up to 50% cases are asymptomatic
- Compresses optic nerve immediately as it passes through optic canal

Dolichoectasia!

- The ICA and optic nerve share a narrow space adjacent to the optic canal
- Enlarged or elongated ICA can force optic nerve against the dural fold of the optic canal
- Risk factors: HTN & DM in older patients
- Sudden or gradual vision loss
- Normal ONH possible, ONH edema also possible
- MRI/MRA is best option; can visualize optic nerve and blood vessel
  - Angiography alone may be normal
Dolichoectasia Treatment Options...
• Microneurosurgical decompression of the optic nerve
  • Frontal approach
  • Remove dural fold of optic canal → escape from ICA pulsations
  • Rule out other causes first: ION, infiltrative disease, NTG
• ***Monitoring – most common
• Neuro-surgical consult recommended

Case #6

Case History
• 62 YO AAF
• CC: “here for my glaucoma check”... (I inherited pt from retiring doctor)
• HPI: vision stable OU, Timolol QAM OU x 2 years, good compliance
• POH: POAG x 2 years by previous doctor
• PMH: [+HTN, +]DM
• Meds: HCTZ, metformin
• ALL: NKDA
• SH: denies all
Exam...

- BCVA: 20/20 OD, 20/25 OS
- CVF: nasal defects OU
- Pupils: PERRL, (−)APD
- EOMs: FROM OU
- SLE: mild NS OU, otherwise WNL OU
- DFE: see pics
- IOP: 20 mmHg OD, 19 mmHg OS via Goldman
- Tmax: 22 mmHg OD, 21 mmHg OS

Baseline photos

1 month later...
Disc hemorrhages...

- "Patients with OCHTN with a disc hemorrhage ‘more frequently developed’ glaucomatous visual field defects than those patients with OCHTN without a disc hemorrhage."

- "Patients with COAG and with a disc hemorrhage have a ‘substantially greater incidence’ of visual field progression compared to patients with COAG without a disc hemorrhage."

**Bottom Line:** Disc hemorrhages are unfavorable prognostic events in OCHTN and COAG

---

**Disc hemorrhages...**

- Associated with localized RNFL defects → **94.4% cases** [1]

- Flame or fan-shaped
  
  - Radial pattern; perpendicular to disc margin [2,3]
  
  - 71% → flame shaped [4]
  
  - 29% → blot shaped [4]

- Most common locations [1]
  
  - 66.7% → inferior temporally
  
  - 29% → superior temporally
  
  - Same areas associated with early glaucomatous damage!

---

**How often are Drance hemorrhages missed on clinical exam?**

- Optic disc hemorrhage = increased risk of POAG conversion
  
  - 84% on FP only vs. 16% clinical exam
    
    - Budenz O, et al. 2006

**Bottom Line:** Drance hemes are easy to miss!

---


Final statement on disc hemorrhages...

- "Disc hemorrhage is associated with increased risk of developing glaucoma and it is a marker for glaucomatous progression."
  - Page 119
- "Consideration of treatment escalation or closer follow-up should be given for patients presenting with optic disc hemorrhages."
  - Page 128

What did we do for this patient?

- Patient already on Timolol QAM OU x 2 years
- Started patient on Latanoprost QHS OU also
- RTC 4-6 weeks for IOP check

Thank you!

- Questions?????
  - cborgman@sco.edu
- Complaints/concerns?????
  - wmcgriff@sco.edu
Plaquenil Toxicity Update

Chris Borgman, OD, FAAO
Assistant Professor
Southern College of Optometry
Memphis, TN

COPE Disclosures:

--I do not have any relevant financial relationships to disclose.
--The content and format of this course is presented without commercial bias and does not claim superiority of any commercial product or service.

Disclosures...

• I have no disclosures to report.
• I’m not perfect...
• I can email you my reference list...
• Questions??
  • Email me: cborgman@sco.edu
Chloroquine (CQ) & Hydroxychloroquine (HCQ)

**Background**

Hydroxychloroquine sulfate

- Chloroquine (CQ) first synthesized in 1930s by Hans Andersag
- Alternative to quinine (found in Peruvian tree bark)
- Original use → combat malaria in WWII
- Less toxic form, hydroxychloroquine (HCQ) developed later
- Started being used in 1950’s, toxicity first noted 1963
  - CQ → 1953 first use
  - HCQ → 1955 first use
- Who's on what in today's world?
  - 1-2% on CQ
  - 98-99% on HCQ


Chloroquine (CQ) vs. Hydroxychloroquine (HCQ)

- Similar molecular structures
- Strong absorption by melanin
- Poor absorption in fatty tissues
- Retinal toxicity: CQ > HCQ
  - HCQ has ↓ tissue accumulation than CQ

Per Dr. Freddy Chang, OD, PhD

• “In the 1970’s, Okun EM, et al. could defect CQ in the RPE layer of rats after 1 single dose. That single dose of CQ was still measureable 5 years later!”


<table>
<thead>
<tr>
<th>Hematologic and dermatological diseases which utilize antimalarial drugs for treatment.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Juvenile dermatomyositis</td>
</tr>
<tr>
<td>Dermatomyositis</td>
</tr>
<tr>
<td>Polyarteritis nodosa</td>
</tr>
<tr>
<td>Polycythemia rubra</td>
</tr>
<tr>
<td>Endomyocardial fibrosis</td>
</tr>
<tr>
<td>Tumefactive tumour lymphoma</td>
</tr>
<tr>
<td>Wegener granulomatosis</td>
</tr>
<tr>
<td>Calcium pyrophosphate deposition disease</td>
</tr>
<tr>
<td>Prophylaxis treatment</td>
</tr>
<tr>
<td>Chronic ulcerative stomatitis</td>
</tr>
<tr>
<td>Dermatopoliosis</td>
</tr>
<tr>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>Scleroderma</td>
</tr>
<tr>
<td>Idiopathic interstitial retinopathy</td>
</tr>
<tr>
<td>Generalized gnathosous-blindness</td>
</tr>
</tbody>
</table>

≥95% cases


<table>
<thead>
<tr>
<th>Many therapeutic MOA’s of CQ and HCQ...</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOA: Decreased formation of peptide-MHC protein complexes required to stimulate CD4+ T cells ➔ down-regulation of the immune response against autoantigenic peptides ➔ immunosuppression!</td>
</tr>
<tr>
<td>*Decreases T-cell receptor calcium signaling ➔ reduces antigen processing</td>
</tr>
<tr>
<td>*Increases pH that interferes with lysosome function ➔ poor antigen presentation</td>
</tr>
<tr>
<td>Inhibits dendritic cells</td>
</tr>
<tr>
<td>Inhibits interferon-Alpha production</td>
</tr>
<tr>
<td>Counteracts neutrophil oxidant production</td>
</tr>
<tr>
<td>Inhibits prostaglandin and cytokine production</td>
</tr>
<tr>
<td>Inhibits autophagy of subset of T-cells ➔ possible use in oncology!</td>
</tr>
</tbody>
</table>

Bottom Line:

- Immunosuppression!

- "HCQ is used mainly in RA and SLE. Most of its benefits have been well described elsewhere, mainly in the context of lupus: reduction of flares and damage, enhancement of MMF response, improvement of survival, and reduced risk of seizures and thromboses... which translates into immunosuppressive, antiproliferative, antithrombotic and photoprotective effects."


Longer survival with HCQ treatment in SLE?

- LUMINA Study (2007)
  - 608 patients with SLE followed over 3+ years
  - 61 total deaths (~10% study population)
    - (+) Plaquenil: 17/61 = 28% deaths
    - (-) Plaquenil: 44/61 = 72% deaths
  - 61% reduction in death rate!

- "It is likely that the use of HCQ in SLE will increase significantly following publication of the LUMINA study, which demonstrated a clear survival benefit of HCQ therapy in patients with SLE."


  We have to be ready for more HCQ patients walking in our doors!

Systemic SE’s of HCQ

- Headache
- Anxiety/depression
- Tinnitus
- GI disturbances
- Skin rashes

OCULAR TOXICITIES:

- Cornea
- Retina

My head says, “Who cares?”
But then my heart whispers, “You do, stupid..."
Quick sidebar...

- Corneal verticillata (whorl keratopathy)
  
  "Chloroquine, and less frequently HCQ, can cause whorl-like intraepithelial deposits (verticillata) in the cornea. These corneal changes are not a direct marker for retinal damage, are not associated with visual loss, and in contrast to retinopathy are usually reversible."  

- Think about:
  - Plaquenil (HCQ)
  - Amiodarone
  - NSAID's (i.e. indomethacin)
  - If a whorl is present with no meds think about Fabry’s Disease!!!!

Symptoms of HCQ retinal toxicity...

- Asymptomatic!
- Decreased/blurry vision
- Central vision loss
- Scotomas
- Reading difficulty
- Glare
- Photopsia
- Metamorphopsia
- Color vision disturbances/reduction

"Visual acuity usually is excellent with either pattern until severe stages of damage, and most patients who develop HCQ toxicity have no visual symptoms at all."  

Retinal HCQ Toxicity
Bull’s Eye Retinopathy!

- “textbook” sign of HCQ and CQ toxicity is a ring of depigmentation near the foveal center
  - Ring scotoma too
- “...the idea that these findings are “characteristic” comes from older literature and a time when retinopathy was not easily confirmed until a bull’s eye was visible. With automated fields and modern imaging technology, unmistakable signs of toxicity can be recognized years before the bull’s eye stage is apparent and before the patient has any visual symptoms. Bull’s eye retinopathy is actually a rather late and severe stage of damage that should not be seen at all with proper management.”

MOA of retinal toxicity...

- Exact pathophysiology – poorly understood & elusive
- “The actual mechanism of retinal toxicity is not well established. Primate studies suggest that the earliest detectable changes are in the neural retina (specifically ganglion cells and photoreceptors), with RPE changes occurring later. In vitro studies on cultured RPE cells suggest that HCQ alters RPE lysosome pH, resulting in higher levels of lipofuscin, a type of pigment that commonly accumulates with age and is associated with photoreceptor degeneration.”

- Can we simplify this please?!
  - RPE lysosomal disruption → accumulation of lipofuscin → photoreceptor degeneration

Why the “ring” or paracentral pattern of toxicity?

- We don’t know!
- “It is currently unclear why the photoreceptors in the parafovea/perifovea are most vulnerable to the toxic effects of HCQ seen clinically.”
What retinal layers are we actually worried about?

Which retinal layers are most affected?

• “Although the mechanism of HCQ toxicity is unclear, as animal experiments have shown the drug can affect all retinal layers, the damage observed in clinical imaging is primarily to the outer retina.”

But, where does pathology/toxicity actually start in the retina?

• Based on work by Rosenthal in 1978!
  • Ganglion cell layer!

• “The exact mechanism of retinal toxicity is still under investigation. Despite the evident clinical changes in retinal pigmented epithelium (RPE) when the maculopathy is already visible, studies in animals after long exposure to chloroquine demonstrated that the first site of damage is most probably the ganglion cell layer.”

Begs the question...should we be screening GCC/IPL on all Plaquenil patients?
Q: So...should we use start using GCC thickness in HCQ toxicity screenings???

A: My humble opinion → Not at this time
• Something to keep an “eye” on though! (pun intended!)

Summary Pathophysiology

Clinical Bottom Line: focus on PIL/RPE junction!

Stats for HCQ Toxicity
Old vs. New: What do we know?

<table>
<thead>
<tr>
<th>Old/Historical</th>
<th>New Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall toxicity prevalence</td>
<td>1.5% patients &gt;5 yrs HCQ use</td>
</tr>
<tr>
<td>Patients that are overdosed</td>
<td>Up to 12%</td>
</tr>
<tr>
<td>Ideal body weight vs. actual body weight</td>
<td>IBW</td>
</tr>
<tr>
<td>Daily dose considered toxic</td>
<td>≤5.5 mg/kg/day (IBW)</td>
</tr>
<tr>
<td>Daily dose considered non-toxic</td>
<td>≥6.5 mg/kg/day (IBW)</td>
</tr>
<tr>
<td>Cumulative dose thresholds</td>
<td>&gt;1000 g</td>
</tr>
<tr>
<td>Age</td>
<td>&gt;60 years</td>
</tr>
</tbody>
</table>


Risk Factors for HCQ Retinopathy

- **Daily dose**
- Duration of use
- *Cumulative dose*
- Renal disease
- Concurrent tamoxifen use → new!
- Lower body weight

Non-Risk Factors:
- Age
- Sex
- Race
- Indications for HCQ (SLE vs. RA, etc.)
- ARR? N/PDR?


New Thoughts:
Ideal Body Weight vs. Actual/Real Body Weight??

- ABW → correlates better with retinal toxicity
- ABW → simpler to calculate
- Less risk of overdosing thin/nonobese patients with ABW

“We propose the use of real body weight for dosage calculation because it correlates better with retinal toxicity than ideal body weight and allows estimations of risk that are independent of body habitus... Maintaining daily use at 5.0mg/kg or less would keep both the cumulative risk and annual risk of retinal toxicity low, especially for the first 10 years of use.”

Toxicity Risk: Daily Dose

- Based on Ideal Body Weight (IBW):
  - >6.5 mg/kg/day HCQ is typical of retinal toxicity, historically
  - ≤6.5 mg/kg/day HCQ considered safe, historically

- Based on Actual Body Weight (ABW):
  - >5.0 mg/kg/day HCQ = increased risk of toxicity
  - ≤5.0 mg/kg/day HCQ = lower risk


Toxicity Risk: Daily Dose

- Historically, is considered rare with doses of
  - Prevalence of toxicity: 0.5% - 2.0% in long-term users (~1% estimation)
  - ~20% risk if on medication for 20 years

- Newer research suggests higher risk! (3x higher than historically thought)
  - 7.5% long-term users
  - Based on 2361 pts in Kaiser Permanente medical database on HCQ (2014)
    - All 2361 pts had been on HCQ ≥5 years
    - Used 10-2 VF’s and SD-OCT
    - 177 of 2361 pts showed clear signs of retinal toxicity → 7.5% pts
    - Only 31 of 177 had a true “bull’s-eye” retinal lesion → confirms higher sensitivity of screening techniques

How many people on HCQ are overdosed?

  - n=675 patients on HCQ
  - 56% females/46% males → overdosed!

- Wolfe F, Marmor MF. Arthritis Care Res (Hoboken). 2010
  - n = 3995 patients on HCQ
  - 53.6% patients → overdosed

  - 30% patients overdosed based on IBW
  - 10% patients overdosed based on ABW

Note the difference when using IBW vs. ABW!!!

Of those that develop HCQ toxicity, how many are overdosed?

  - n=121
  - 11.6% patients developed toxicity (n = 14/121)
  - 78.6% (n=11/14) were overdosed

  - n=123
  - 13.8% developed toxicity(n=17/123)
  - 76% were overdosed (n=13/17)

Notable quotes on overdosing!

- “Rheumatologists should focus on the recommended dosage of HCQ ≤5 mg/kg/day and start regular ophthalmologic screening according to the risk factors.”

- “…we recommend that all patients using HCQ keep daily dosage <5.0 mg/kg real weight. Following this guideline will minimize the risk of retinopathy and allow long-term use of HCQ for most patients.”
The Calculation: Daily Dosing

\[
\frac{\text{Body Weight (lbs)}}{2.2 \text{ lbs}} = \text{weight in kilograms}
\]

\[
\text{Total daily dose (mg)} \times \frac{1}{\text{body weight (kg)}} = \text{dose of mg/kg/day}
\]

Example of daily dose calculation...
• 50 YO WF with history of RA
• Weighs 140 lbs (ABW)
• Takes HCQ 200 mg BID PO \( \rightarrow \) 400 mg/day

\[
\frac{140 \text{ lbs}}{2.2 \text{ lbs}} = 63.63 \text{ kg}
\]

\[
400 \text{ mg/day} \times \frac{1}{63.63 \text{ kg}} = 6.29 \text{ mg/kg/day}
\]

Another example of daily dose calculation...
• Same 50 YO WF with history of RA
• Weighs 140 lbs (ABW)
• Takes HCQ 200 mg BID every other day \( \rightarrow \) 300 mg/day

\[
\frac{140 \text{ lbs}}{2.2 \text{ lbs}} = 63.63 \text{ kg}
\]

\[
300 \text{ mg/day} \times \frac{1}{63.63 \text{ kg}} = 4.71 \text{ mg/kg/day}
\]
Toxicity Risk: Duration of Use

<table>
<thead>
<tr>
<th>Dose</th>
<th>Duration</th>
<th>Toxicity Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;5.0 mg/kg/day</td>
<td>10 yrs</td>
<td>8%</td>
</tr>
<tr>
<td>&gt;5.0 mg/kg/day</td>
<td>15 yrs</td>
<td>20%</td>
</tr>
<tr>
<td>&gt;5.0 mg/kg/day</td>
<td>20 yrs</td>
<td>40%</td>
</tr>
<tr>
<td>4.0 - 5.0 mg/kg/day</td>
<td>10 yrs</td>
<td>&lt;2%</td>
</tr>
<tr>
<td>4.0 - 5.0 mg/kg/day</td>
<td>15 yrs</td>
<td>6.5%</td>
</tr>
<tr>
<td>4.0 - 5.0 mg/kg/day</td>
<td>20 yrs</td>
<td>20%</td>
</tr>
<tr>
<td>&lt;4.0 mg/kg/day</td>
<td>10 yrs</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>&lt;4.0 mg/kg/day</td>
<td>15 yrs</td>
<td>&lt;2%</td>
</tr>
<tr>
<td>&lt;4.0 mg/kg/day</td>
<td>20 yrs</td>
<td>6%</td>
</tr>
</tbody>
</table>


Toxicity Risk: Cumulative Dose

- **>1000 g HCQ lifetime dose** = highest risk!
- Same as it’s been forever!
- One study reported 86% of patients with HCQ toxicity had cumulative dose >1000 g

Marmor et al. Ophthalmol. 2016 → Updated plaquenil guidelines

How do you calculate cumulative dose again?

- Same patient as before….
- 50 YO WF with RA on Plaquenil 200 mg BID x 10 years
  - 200 mg BID = 400 mg daily
  - 400 mg x 365 days = 146 g/year
  - 146 g x 10 years = 1460 grams total!
  - 200 mg BID every other day = 300 mg daily
  - 300 mg x 365 days = 109.5 g/year
  - 109.5 g x 10 years = 1095 grams total!
Toxicity Risk: Lower Body Weight
- Poor distribution in fatty tissues ➔ hence initial IBW recommendations for dosing
- Obese patients can be overdosed more easily!
  - ≤ 6.5 mg/kg of ideal body weight = old recommendation
  - ≤ 5.0 mg/kg of real body weight = new recommendation
- Obese patients can be overdosed more easily!
- ≤ 6.0 mg/kg of ideal body weight = old recommendation
- ≤ 5.0 mg/kg of real body weight = new recommendation

Toxicity Risk: Renal Disease
- Main clearance location for plaquenil = kidneys
- 50% decrease in renal function = 2x toxicity risk!
- Partially cleared by liver ➔ No increased risk with concomitant ↓ renal function

Toxicity Risk: Tamoxifen Use
- 5x greater risk of HCQ toxicity!
- MOA: unclear; synergistic retinal toxicity?

***Summary of HCQ Risk Factors***

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Increased HCQ Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Daily dose</strong></td>
<td>&gt;5.0 mg/kg/day (ABW)</td>
</tr>
<tr>
<td><strong>Cumulative dose</strong></td>
<td>&gt;1000 g lifetime</td>
</tr>
<tr>
<td><strong>Duration of use</strong></td>
<td>&gt;5-7 years (~20% risk after 20 yrs of Tx)</td>
</tr>
<tr>
<td><strong>Renal disease</strong></td>
<td>(+) 2x increased risk</td>
</tr>
<tr>
<td><strong>Tamoxifen use</strong></td>
<td>(+) 6x increased risk</td>
</tr>
<tr>
<td><strong>Obesity/Overweight</strong></td>
<td>(+)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>(-) per 2016 AAO guidelines</td>
</tr>
</tbody>
</table>

New Screening Guidelines in 2016!


Why the new updates to the 2016 guidelines?

• “Despite the existence of published guidelines, screening practices often have been inconsistent or deficient...The recommendations in this revision are more concise and practical than the prior version, to encourage wider compliance.”

Goal of screening?

• The AAO recently proposed screening recommendations for HCQ retinopathy. These recommendations state that the goal of screening for HCQ retinopathy is not to discontinue the valuable drug when there are borderline abnormalities, but to recognize definitive signs of toxicity at an early enough stage to prevent vision loss.

• Although it is important to be sensitive to signs of damage in a typical pattern, it is also important to verify such signs with more than 1 test or by repeat testing.”

When should annual screenings start?

• Baseline testing recommended pre-HCQ initiation
  • Or within 6-12 months of start date!

• “Given the initial low risk of HCQ or CQ retinopathy, with a proper dose and in the absence of major risk factors, annual screening can be deferred until there has been 5 years of exposure.”

• When should annual screenings begin?
  After 5 years of HCQ treatment
  Or
  When 1000 gram threshold is met

Who is actually getting screened?

• Study location: Michigan
• Study time period: 10 years (2001-2011)
• 6339/18,051 patients with RA/SLE treated with CQ/HCQ
  • 35% taking CQ/HCQ
• 1409/6339 patients were on CQ/HCQ for ≥4 yrs
• 8% on CQ/HCQ ≥4 yrs
• Among the highest-risk patients:
  • Only 28% had regular eye care visits
  • 6% had no eye exams
  • 35% had no diagnostic testing
• Bottom Line: medicine needs to improve HCQ screening methods!

Screening Tests?
**Recommended screening tests...**

<table>
<thead>
<tr>
<th>Recommended Screening Tests</th>
<th>1. 10-2 VF</th>
<th>2. SD-OCT</th>
<th>3. FAF</th>
<th>4. mfERG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular History</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Anterior Chambers</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Gonioscopy</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Angle Closure</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Biomicroscopy</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>OCT (en face)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>FAF</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>mfERG</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>“Unless toxic changes are advanced and obvious, at least 1 objective test should confirm subjective findings before toxicity is diagnosed.”</td>
<td>Marmor MF, et al. Ophthalmol. 2016.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**General signs of HCQ toxicity to look for...**

- Parafoveal abnormalities on FAF and SD-OCT
- Bilateral perifoveal scotomas in VF 10-2
- Depigmentation seen on fundoscopy
- Bilateral paracentral mfERG depression

All the above are indicative of "probable" and potentially irreversible change

> "...retinal toxicity should be diagnosed on the basis of alterations in at least 2 tests..."  


**Color Photos vs. FAF**

- **Color Photos:**
  - Not used anymore for screening purposes but can be baseline
  - 100% eyes in unaffected group labelled as normal
  - ~52% of affected patients were labelled as normal (oops!)

- **Fundus autofluorescence (FAF):**
  - FAF is a good screener but not perfect
  - 92% eyes in unaffected group labelled as normal
  - 26% of affected patients were labelled as normal (oops!)

Don't use color photos or FAF alone for screening purposes!

Recommended screening tests...

1. 10-2 VF
2. SD-OCT
3. FAF
4. mfERG

"Unless toxic changes are advanced and obvious, at least 1 objective test should confirm subjective findings before toxicity is diagnosed."

Visual Field Testing...

- SITA 10-2 is most common ancillary test used for HCQ since early 1990’s
  - White-on-white recommended
  - Most at risk areas: between 2°-6° degrees from center of the field
  - Toxicity → partial/full ring scotomas involving parafoveal region
- New finding: 24-2/30-2 in Asian patients!
- Central visual acuity usually preserved until late stages of toxicity
- Suspicious findings with 10-2 to warrant further investigation:
  - Cluster of scotoma points in the 2°-8° degree zone
  - Scotoma that persists and grows in depth/breadth
  - Appearance of new scotomas

Common 10-2 VF defects from HCQ toxicity...

Characteristic Ring Scotomas
Central scotomas
Central visual field defects

**VF’s**

- What is most common VF encountered?
  - “The most frequent regions of the retina showing early damage are inferotemporal, with a corresponding superonasal field defect, but this is not absolute.”

- Very sensitive test in reliable patients
- High variability between visits
  - Some studies show 30% of VF’s are unreliable!
- Uncertain tests? → repeat!
  - Uncertain tests? → correlate with objective testing!

**Recommended screening tests...**

1. 10-2 VF
2. SD-OCT
3. FAF
4. mfERG

“Unless toxic changes are advanced and obvious, at least 1 objective test should confirm subjective findings before toxicity is diagnosed.”

**SD-OCT**

- Central VFs and SD-OCT most widely used combination of testing
- Widely available and used among practitioners
- Typical findings on OCT scans:
  - Focal disruption of outer retina >> widespread thinning

- Typical findings on OCT scans:
  - Occur in parafoveal locations!
  - Thinning/loss of:
    - Photoreceptors
    - ORL
    - Ellipsoid zone (OIS junctions)
    - RPE

In patients with plaquenil toxicity:
- 84% had discontinuity/loss of ellipsoid zone
- 3 patients did not have this...
- 0% of unaffected patients

Interesting insight:
- Thinning of the inner inferior subfield can serve as a useful objective screening tool for possibility of HCQ toxicity
- <305 µm would capture all affected individuals, only 25% normal
- 100% sensitivity, 25% specificity → not too bad...

Recommended screening tests...

1. 10-2 VF
2. SD-OCT
3. FAF
4. mfERG

“Unless toxic changes are advanced and obvious, at least 1 objective test should confirm subjective findings before toxicity is diagnosed.”

**Fundus autofluorescence (FAF)**

- Identified cellular breakdown products (accumulations of lipofuscin) in the RPE
- Often equivocal in early stages of toxicity; difficult to use!
- Useful in showing extent and progression of toxicity once present

> “Fundus autofluorescence had a statistically significant lower proportion of positive test findings than mfERG. This suggests that FAF may be most effective for following the progression of retinal changes, as opposed to being used as an early screening tool.”

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**FAF: Hyper vs. Hypo in HCQ toxicity...**

- **Hyperautofluorescence**
  - Photoreceptor and RPE cellular stress
  - "Sick" cells
  - Accumulation of lipofuscin

- **Hypoautofluorescence**
  - Photoreceptor and RPE cell loss
  - Absence of RPE

- In HCQ toxicity: hyperfluorescence before hypofluorescence

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**Bilateral increase in parafoveal AF**

**Widespread increased AF signal, and patchy decreased AF signal parafoveally**

**Very minimal changes in AF**

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"...bull’s eye maculopathy visible on near-infrared reflectance imaging may be an additional objective sign of early HC toxicity and, of possible importance, that this sign may disappear with late HC toxicity."

"...unless toxic changes are advanced and obvious, at least 1 objective test should confirm subjective findings before toxicity is diagnosed."

**Recommended screening tests...**

1. **10-2 VF**
2. **SD-OCT**
3. **FAF**
4. **mfERG**

**mfERG**

- Objective/functional test
- Highly sensitive for macular dysfunction
- Local topographical ERG responses
  - Reflects damage at or before bipolar cells
  - Paracentral ERG depression → amplitude loss!
- Not widely available
- Significant expertise needed to perform and interpret accurately
- Long testing time
- Average amplitude measured as: (P1-N1)
- Definition of toxicity via mfERG alone:
  1. Increased R1 to R2 ratio (>99% confidence limits)
  2. Reduced R1 absolute amplitude (<99% confidence limits)
**Best time to use mfERG??**

- "Multifocal ERG may provide objective, functional evidence of disease, and may be useful when the diagnosis of HCQ is uncertain: in particular when visual field analysis demonstrates scotomata in the absence of structural evidence on SD-OCT or AF."
  

- VF defect, but normal SD-OCT/FAF? → think mfERG!

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**What is the best single test?**

**What is the best combination of tests?**

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**Sensitivity and specificity of the tests**

- Notice → Combos are more sensitive than either test alone

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD-OCT</td>
<td>78.1</td>
<td>78.1</td>
</tr>
<tr>
<td>HD-OCT</td>
<td>72.4</td>
<td>64.7</td>
</tr>
<tr>
<td>mfERG</td>
<td>67.2</td>
<td>67.2</td>
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<tr>
<td>mfERG + HD-OCT</td>
<td>73.3</td>
<td>73.3</td>
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<tr>
<td>mfERG + SD-OCT</td>
<td>75.7</td>
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</tr>
<tr>
<td>HD-OCT + mfERG + SD-OCT</td>
<td>60.0</td>
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</tr>
</tbody>
</table>

*Abbreviations*:

- VF: visual field
- FAF: Fundus autofluorescence
- SD-OCT: Spectral domain optical coherence tomography

Structure vs. Function: what happens first?

- **Structure first, function second:**

- **Function first, structure second:**

- **~90% of cases**
- **~10% of cases**

- Evidence for both!
- Structure before function usually!
- Rely on totality of evidence to make a decision!

Screening Costs?

**Cost of screening for HCQ toxicity?**

- "...revisions in the AAO hydroxychloroquine screening guidelines from the 2002 version to its current revised 2011 version resulted in a 40% increase in total associated health expenditure costs, rising from an estimated $29 million to $40.7 million."

How good are medical professionals at following AAO guidelines?

Estimated HCQ Screening Adherence Patterns...

- Study location: Cole Eye Institute, Cleveland, Ohio
- n = 1294 HCQ screenings
  - Used 2011 HCQ Screening Guidelines
- Most common screening tests: OCT & HVF 10-2
  - 50% (648/1294) → appropriate screening
  - 27% (348/1294) → underscreened
  - 23% (299/1294) → inappropriately screened
  - 50% HCQ screenings were inadequately screened in this study!


HCQ Retinal Toxicity Severity
Gold standard for definition of HCQ toxicity?

• "In studies in which the sensitivity and specificity is to be determined, a gold standard against which the tests will be graded must be defined. For the purposes of this work the definition of hydroxychloroquine retinopathy (the gold standard) was that the drug was discontinued by the ophthalmologist and the prescribing physician because retinopathy was considered to be present based on the totality of the clinical evidence. This gold standard has been used before." 


Normal → Early/Mild → Moderate → Severe →


Management of HCQ Toxicity?

Management of retinal toxicity...

- No treatment available!
  - Off-label use of lutein/zeaxanthin (AREDS) has been discussed by some doctors (???)

- Identify earliest sign of toxicity and d/c med ASAP

- Call prescribing physician to initiate process

- Do not d/c med without consulting with prescribing physician first

- My recommendation ➔ Send a follow-up letter for a "paper trail"

"But we must emphasize that the drugs should not be stopped for questionable or ambiguous signs of damage. Such findings should trigger retesting, or testing with additional procedures such as mfERG, or perhaps an earlier follow-up visit. One should have unequivocal abnormalities or corroborative evidence of toxicity before making a diagnosis of retinopathy and stopping a very good drug."

Let’s say it again!

• “If the diagnosis of maculopathy is equivocal, screening every 3 to 6 months for the confirmation of toxicity is advised.”

• “This drug should typically be discontinued once toxicity is clearly evident, but the progression of damage is slow enough to repeat borderline or questionable tests, or order additional tests for confirmation, so that a useful medication is not stopped unnecessarily.”
  - Marmor MF, Melles RB. JAMA. 2015.

Progression after D/C?

Progression can occur after discontinuation!

Up to 3 years post-D/C per some articles!

Miscellaneous Topics
-- Subset of HCQ in Asian populations
-- HCQ blood draws
-- HCQ & Pregnancy
-- HCQ in cancer patients

New subset of HCQ in Asian patients?

Pericentral toxicity quote...

• “Examiners should look critically at the edge of 10-2 fields, SD-OCT scans, and standard FAF images for hints of more peripheral damage. When possible, widefield FAF should be obtained, and 30-2 fields may be indicated in addition to 10-2 fields. The mfERG extends in most laboratories to 20 degrees of eccentricity or more and may show a pattern of peripheral rather than parafoveal loss.”

New Topic: Should HCQ be monitored with regular blood draws?

- No!

- Blood concentrations of HCQ can vary more than 10-fold among compliant patients receiving similar doses.....whoa!

- "...blood levels are not reliable for assessing partial levels of compliance because of the high variability among subjects."

New Topic: HCQ during pregnancy?

- HCQ can cross the placenta
- Cord blood concentrations are nearly identical to maternal blood
- But...numerous studies show safety of HCQ during pregnancy

- "...current evidence suggested no fetal ocular toxicity of antimalarial medications during pregnancy. Accordingly, experts generally recommend continuing HCQ during pregnancy when indicated."

Management after Dx
Management of Retinal Toxicity

- “There is no treatment for HCQ of CQ retinopathy, and despite some hints of early functional recovery in the literature, there is no clear evidence that significant recovery can occur.”

Patient has stopped HCQ...now what?

- “There are no established guidelines for following patients with toxicity.”

- Don’t forget about Low Vision referrals!

Conclusion
My humble approach!

• Baseline exam within 6-12 months of starting HCQ
• Baseline testing includes:
  • 10-2 VF (white-on-white): 24-2/30-2 for Asian populations
  • SD-OCT (mac cube, 21-line raster and/or radial scans, GCC?)
  • FAF
• Yearly exams with DFE
  • Review history & medications (has dose, weight, etc. changed?)
  • Calculate daily dose & total dose
  • No screening tests unless Sn/Sx suggest toxicity or overdose
• Year 5 → start annual screenings with testing
  • 10-2 VF (24-2/30-2 for Asian populations)
  • SD-OCT (mac cube, 21-line raster and/or radial scans, consider GCC?)
• At SCO, Spectralis allows raster & FAF in same scan!
• Year 5 → start annual screenings with testing
  • 10-2 VF   (24-2/30-2 for Asian populations)
  • SD-OCT (mac cube, 21-line raster and/or radial scans, consider GCC?)
• Suspicious/equivocal case??? → mfERG
• Communicate with PCP/Rheumatologist in timely fashion!

Suggested screening protocol...

"The optimal algorithm for hydroxychloroquine toxicity screening using different methods is still being debated."

"There remains no established criterion for diagnosing HCQ toxicity and, as such, the physician must rely on a combination of characteristic functional and anatomic abnormalities to diagnose a patient with HCQ toxicity. An understanding of each screening modality and a keen eye to detect subtle abnormalities is critical to diagnosing early disease."

NAD = no appreciable disease

Billing & Coding

How do I code exam to rule out toxicity?

- Appropriate 99xxx or 92xxx exam code
  - HVF 10-2 (92083)
  - Macula SD-OCT (92134)
  - FP/FAF (92250)
  - Multifocal ERG (92275)

- 1) Rheumatoid Arthritis (M06.9)
  - SLE (M32.9)

- 2) High-Risk Med (Z79.899)

What if patient develops HCQ maculopathy?

- Appropriate 99xxx or 92xxx exam code
  - HVF 10-2 (92083)
  - Macula SD-OCT (92134)
  - FP/FAF (92250)
  - Multifocal ERG (92275)

- 1) Rheumatoid Arthritis (M06.9)
  - SLE (M32.9)

- 2) Toxic maculopathy (H35.38x)
Thank you!!!

Questions??
Accolades??

Email → cborgman@sco.edu

Complaints???

• Email → wmcgriff@sco.edu