Uveitis Update 2017

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Cole Eye Institute

Cleveland Clinic

Cleveland, OH

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So usually when I come to an alumni meeting.

- The reviews are mainly negative
- "I came here to discuss the things that make my day exciting, not the depressing stuff…"
- "I am disappointed that the uveitis lecture did not include more discussion about the use of premium IOLs"
- But every once in a while….
- "The uveitis lecture had a fair amount of jokes about STDs and ulcers….bring him back!"

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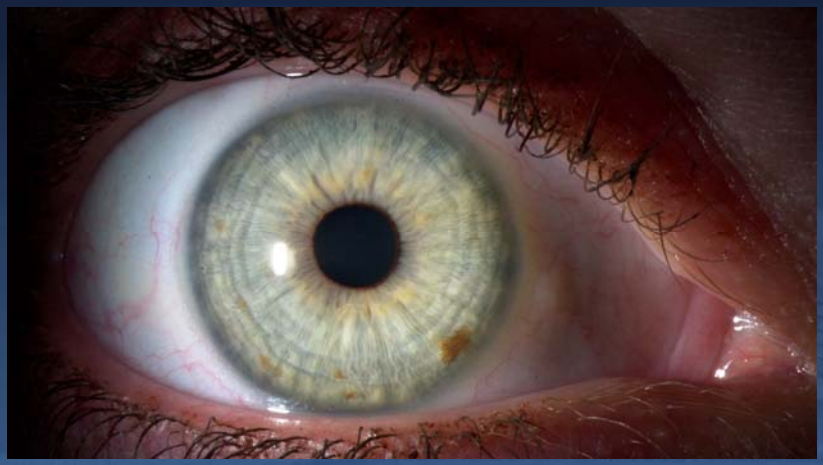
Our Goals as Ophthalmologists



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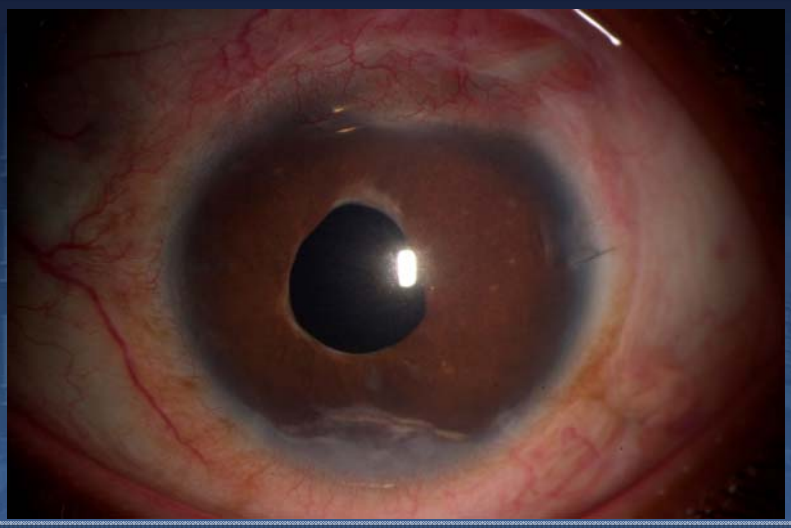
What We Do Not Want



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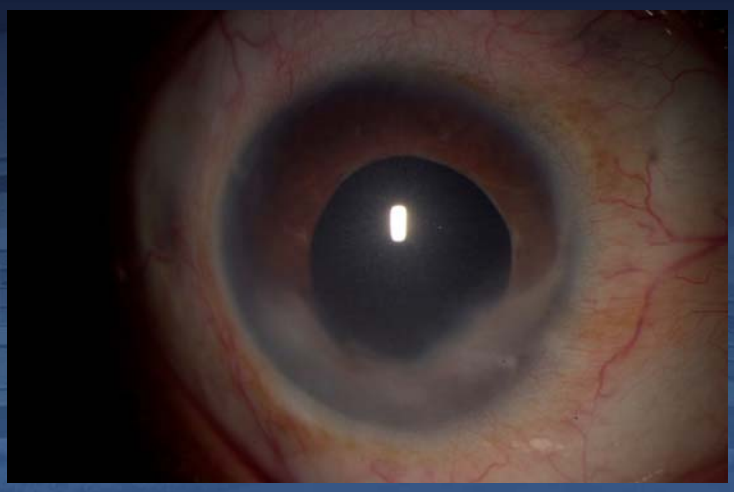
What We Do Not Want



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What We Know

- Severe vision loss occurs in 25%-33% of all uveitis cases
- Repeated bouts of inflammation increase risk of severe vision loss
- High-dose corticosteroids – long term have high rates of morbidity
- Majority of physicians surveyed do not adhere to recommended guidelines to treat uveitis[1]

1. Nguyen Q, et al. Abstract presented at: AAO 2010; October 21, 2010; San Francisco, California. Abstract #PAO37

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Guidelines

- Active uveitis – treat with high dose of corticosteroids[1]
- Add steroid-sparing agent if inflammation cannot be controlled with <10 mg prednisone within 3 months[1]
- Average dose > 30 mg – maintained for average duration of 21 months[2]
- Immunosuppressives only prescribed in 12%[2]

1. Jabs DA, et al. *Am J Ophthalmol.* 2000;130:492-513. (A)
2. Nguyen Q, et al. Abstract presented at: AAO 2010; October 21, 2010; San Francisco, California. Abstract #PAO37

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But most of the time you will not see the wacky things

- So we are not going to focus on the rare posterior uveitis cases
- We are going to address the most common presentation that can give problems

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What we will cover today

- Show some cool cases which highlight
- How to approach the work-up
- How to approach treatment.
- What's my periop regimen?
- How to approach the surgery.
- Post-op inflammation?
- What signs should I worry about?
- Just in case, what's my email address?

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Case Presentation

- 50 year old caucasian female
- 4 year history of anterior uveitis mainly in the left eye
- Here for a second opinion
- Has had previous testing – all of which is negative
- Recalls negative syphilis, TB, and other inflammatory markers. States she is otherwise healthy
- Treated with local steroids (peri-ocular and intravitreal steroids)
- Last one was 1 month ago
- Vision 20/20 OD, 20/150 OS

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Review of systems

- Positive for allergies and occasional wheezing
- Negative for Headaches, N/V, Arthritis, Rashes, history of STDs, Chest pain, SOB, Coughing blood, diarrhea, neuro symptoms, ulcerations in mouth or other areas.

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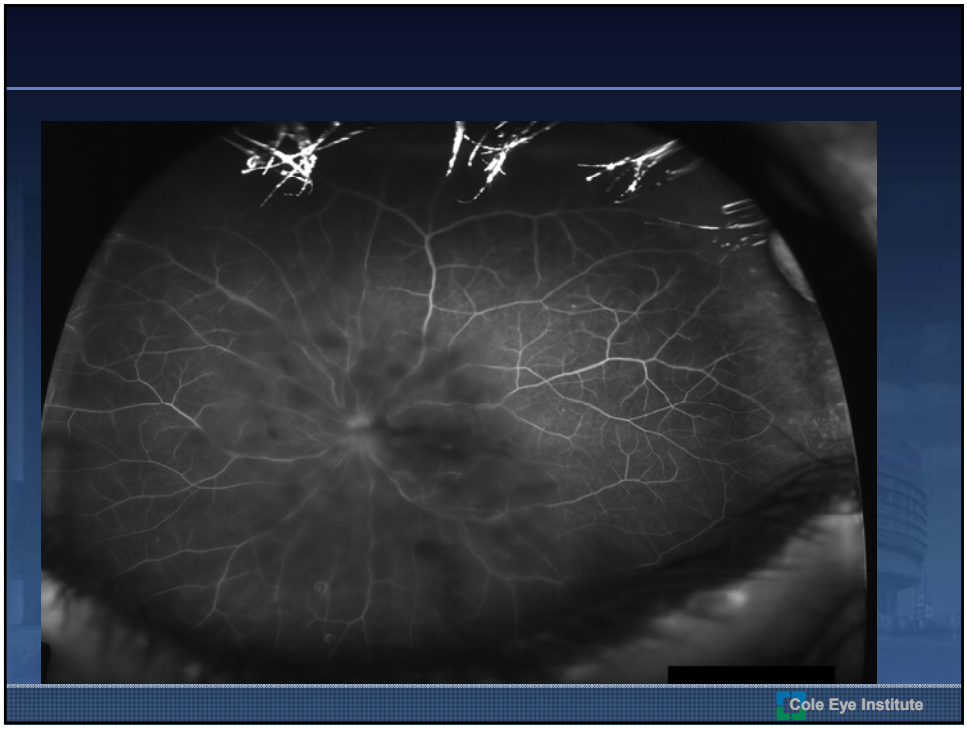
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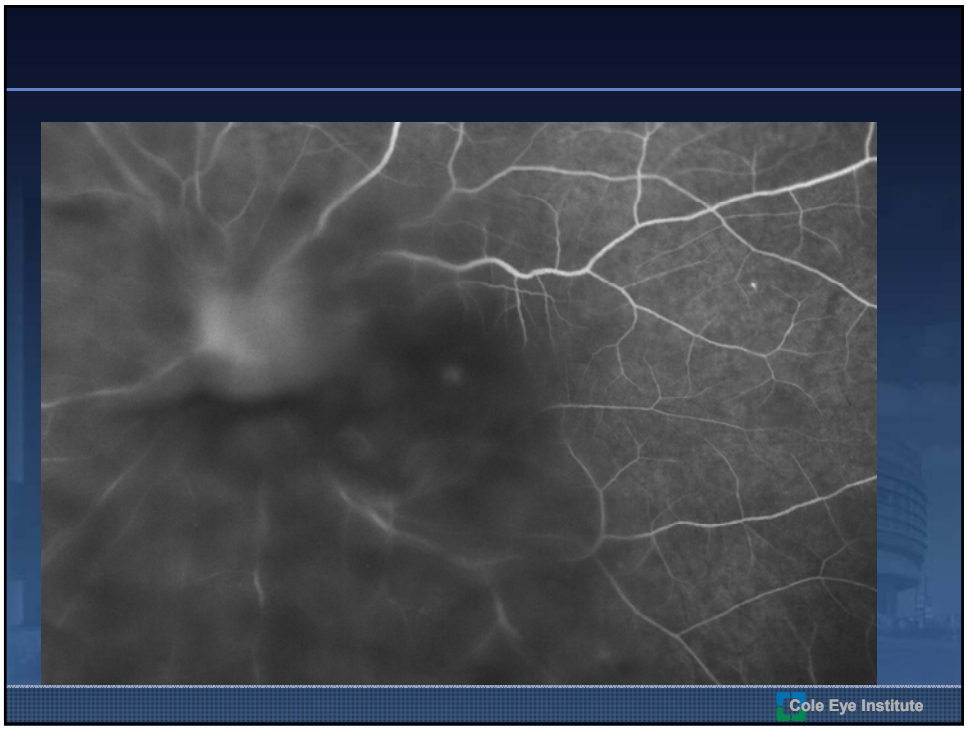
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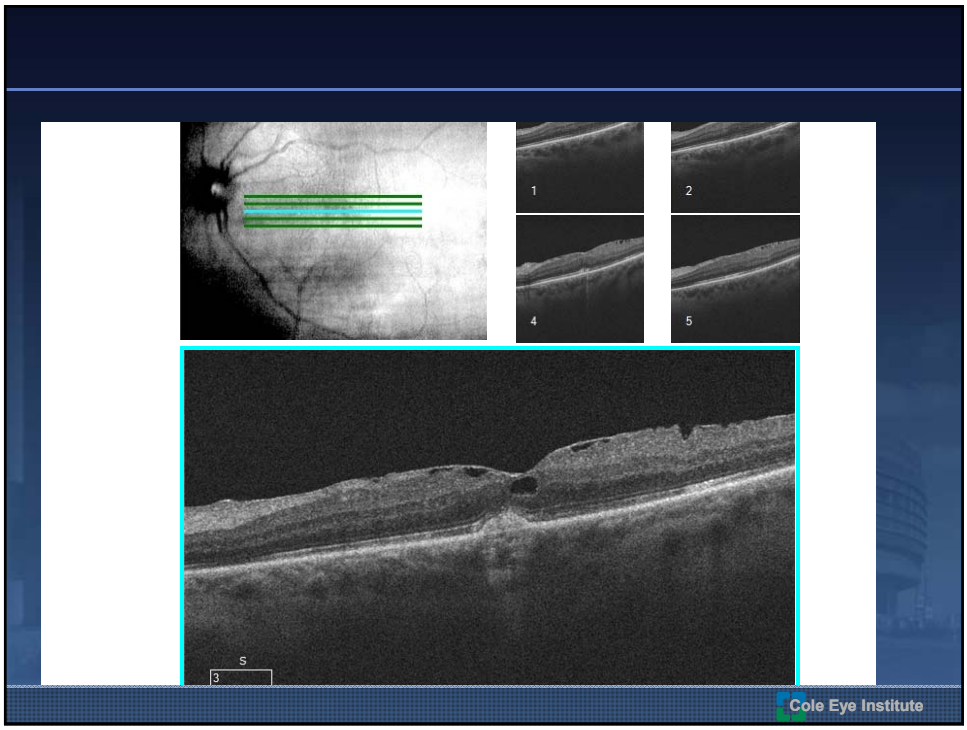
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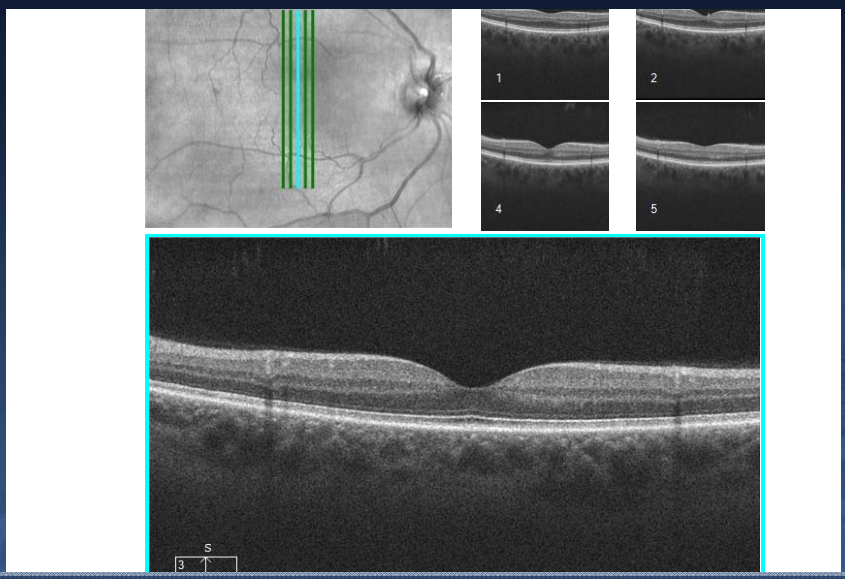

Thoughts?

- Chronic intermediate uveitis OS>OD
- Not much on FA
- Fellow sees patient – comes out of room with
- Differential Diagnosis:
- MS, IBD, TB, Sarcoidosis, Syphilis, Lyme disease (she is from Pennsylvania)
- Should I re-test her?
- How about treatment?

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My super nurse/research coordinator/therapist Kim

- Kim walks into the room and then walks out and makes the diagnosis
- What did she find?
- Audible wheezing, struggling to talk and answer questions
- Kim: “Dude, she has sarcoidosis”
- Fellow: “I thought she just had a sexy raspy voice”
- Me: Deep sigh….

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- ACE – 73
- Chest CT:
- Multiple mediastinal and peribronchial enlarged lymph nodes, some as large as 20 mm
- Biopsy performed – positive for non-caseating granulomas
- Dx - sarcoidosis

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Lesson

- Previous negative work-ups warrant a rethinking and possible work-up
- Sarcoidosis occurs in Caucasians
- Listen to your patient – really listen…..

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Case Presentation

- 33 year old male
- 4-6 week history of blurred vision left eye
- History of Crohn's disease
- Dx with anterior uveitis
- HLA b27 +
- Treated with topical PF
- On infliximab every 4 weeks

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Case Presentation

VA OD 20/25 OS 20/70

1+ cells 4+ cells

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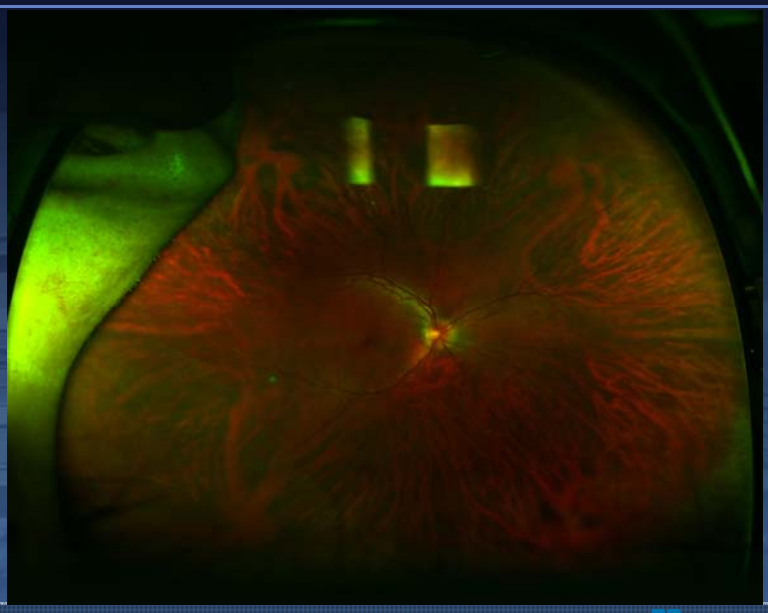

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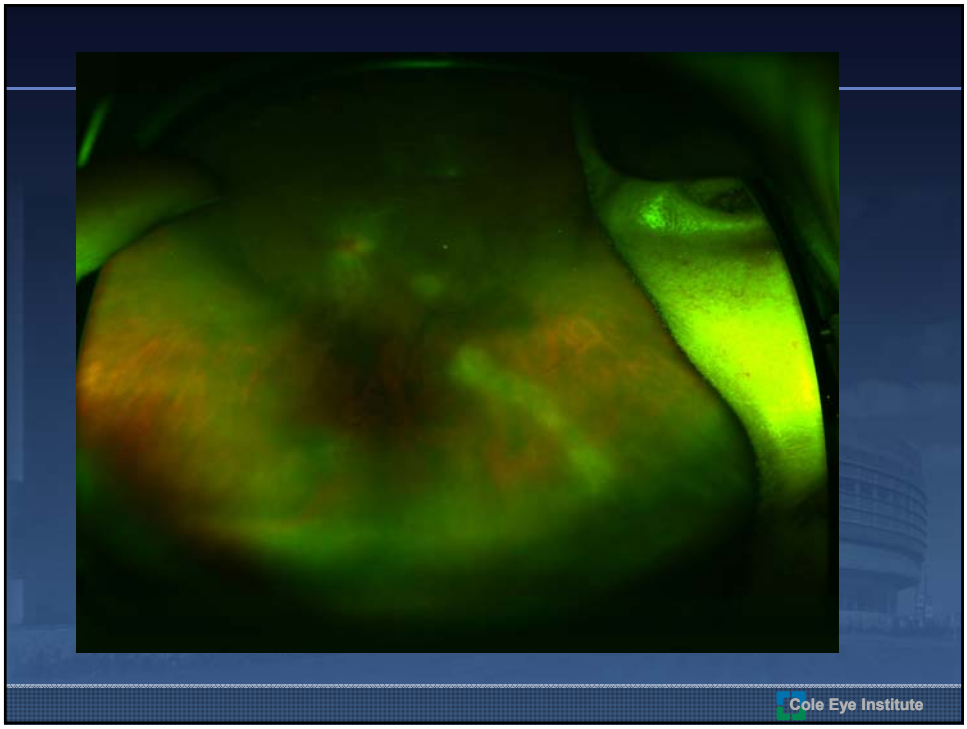
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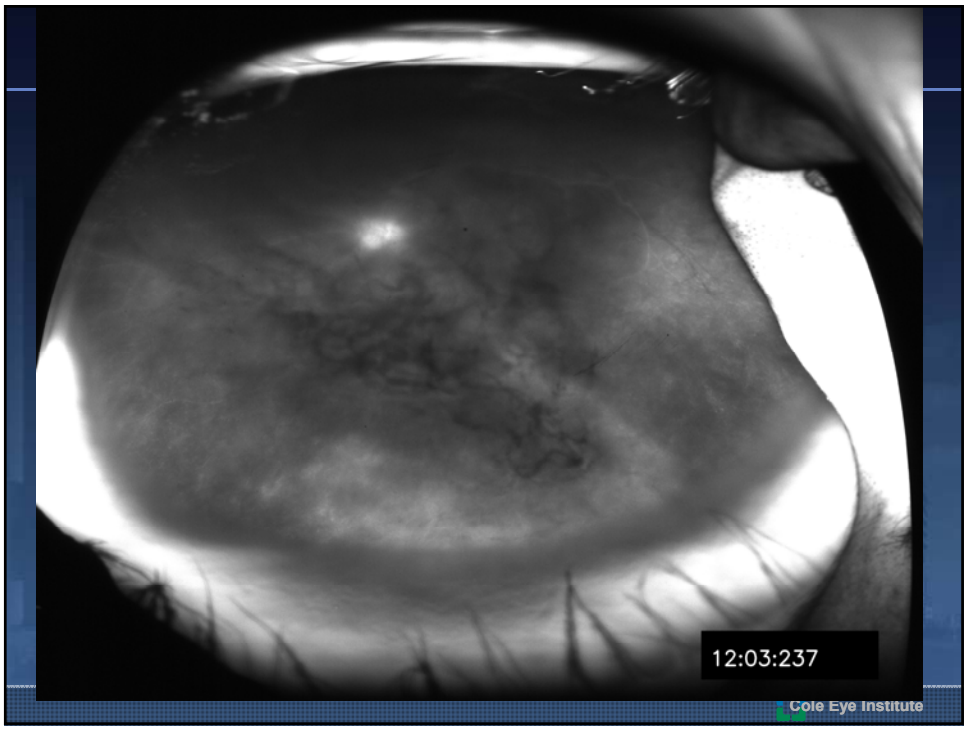
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Case Presentation

- 33 year old male
- History of Crohn's disease
- B27+
- With Intermediate uveitis - ?posterior uveitis
- On infliximab
- Is this a common form of uveitis in IBD?
- What should we do now?
- Start prednisone?

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Case Presentation

- Prednisone?
- I am already on prednisone doc!
- For my Crohn's!
- I thought you wanted to know my medications for my eyes only!
- Are you more worried or less worried now?
- Active inflammation on infliximab and prednisone

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Case Presentation

- Labs drawn
- Toxoplasmosis IgG and IgM – negative
- Syphillis IgG positive, RPR positive 1:128
- Patient called and informed of results
- Doc, how did I get syphillis?
- Referred pt to chairman Dr. Dan Martin, world renowned expert on the process of spontaneous spirochete infection
- Syphilis = the immaculate infection

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Case Presentation

- Treated with
- Aqueous PCN G 24U IV daily for 4 weeks

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Syphilis

- Can present in the eye as anterior uveitis, intermediate uveitis or posterior/panuveitis
- Rank of cases in 2015
  - San Francisco, CA 516 cases, 60.5/100,000
  - Cleveland-Elyria, OH – 199 cases, 9.6/100,000

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Demographics of syphilis in US

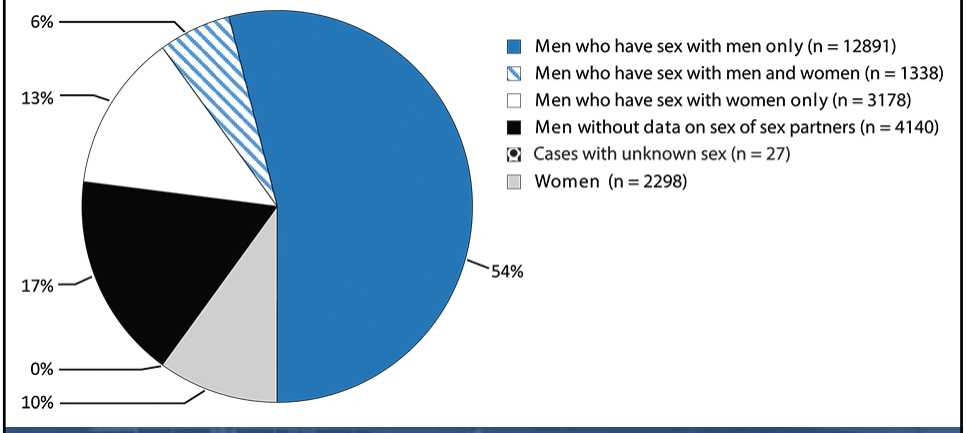

Image Source: Figure 40 from STD Surveillance 2015

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Syphilis Diagnosis and Treatment

- Diagnosis
  - Treponemal test (FTA-Abs, Syphilis IgG) followed by non-treponemal (RPR, VDRL)
- Treatment
  - Neurosyphilis
  - IV PCN for 14 days or IM daily with po probenecid
- The difference between po prednisone and intravitreal steroids

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Lesson

- Even inflammatory disease patients can get infectious disease
- Patients who don't respond to immune suppression (prednisone) – reconsider diagnosis
- Syphilis – enough said

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When should I order testing

- No hard and fast rules
- Anterior Uveitis – hypopyon associated, First episode?
- Is it really anterior uveitis?
- All other types – ordering at first evaluation
- Please remember – to talk to your patient and perform a ROS.
- In our previous talk - you may need imaging to help you

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What should I order?

- Think about your population and your patient (ROS), in my clinic I have a large amount of infections and sarcoidosis.
- Recurrent anterior uveitis I consider:
  - FTA-Abs/Syphilis IgG, Quantiferon Gold, ACE, CXR, HLA B27
  - Urine B-2 microglobulin for children (consider ANA in kids as well)
  - Consider AC tap for viral PCR
- For posterior/panuveitis
  - infectious – Toxo, Bartonella depending on the presentation
  - HLA-A29 if concern of birdshot
  - Chest CT if suspicious for sarcoidosis
  - Tissue biopsy in elderly or if concerned about infectious disease

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Case Presentation

- 68 year old female with h/o CNV secondary to POHS vs AMD in both eyes presents for second opinion of recurrent iritis left eye
- Gets Avastin for CNV both eyes
- Has been treated with pred forte
- Recurs every time it is stopped
- Workup negative including HLA B27, Q-gold, RPR, ACE, ANCA, ANA, CMP, CBC, Lyme
- Had previous “uncomplicated cataract surgery”

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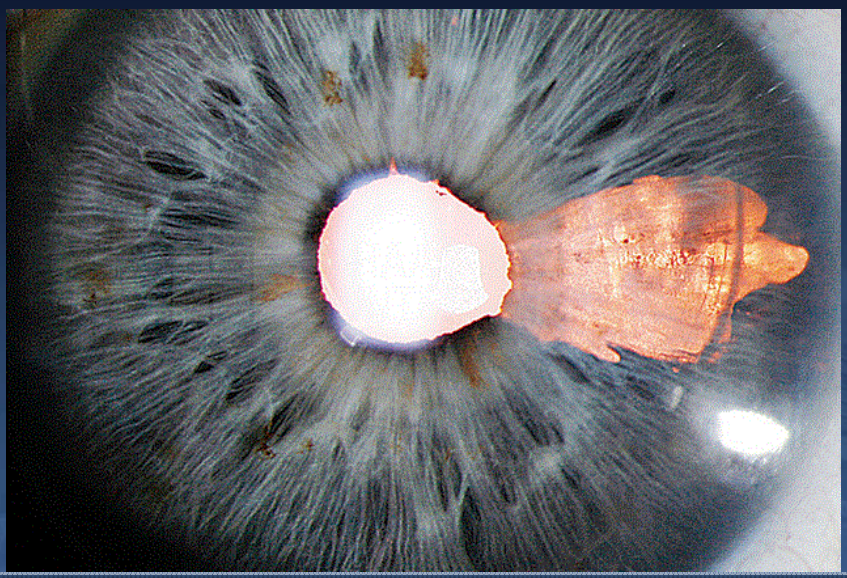

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Case Presentation

- Left eye has 2+ cell, pigment diffusely on endothelium, and sectoral iris atrophy with iris transillumination defects
- On Lotemax QID because of IOP response to pred forte
- Also notes that her eye pressure has been high in the past even when she was not on steroid drops
- Other questions?
- Previous zoster infection
- Yes around the face
- AC tap – positive for VZV

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Pearls for viral anterior uveitis

- Unilateral disease
- Episodes of IOP spikes
- KP or pigment on endothelium diffusely
- Iris atrophy or transillumination defects
- Iris dilation without dilating drops
- Topical antivirals don't really help
- Systemic antivirals needed for treatment and prevention
- Chronic therapy of both anti-viral and some topical steroid

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Diagnostic Procedures

- Tips
  - Prior to procedure – know who is receiving the sample
  - Recognize you have limited sample – choose your test wisely
  - Be prepared for the unexpected..
- When to perform
  - When the clinical situation does not respond as expected
  - There is tissue to biopsy
  - Malignancy and/or infection is of concern

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Be Aware of this Potential

Source: Am J Clin Pathol © 2007 American Society for Clinical Pathology

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Your Biopsy - processed

FLOW CYTOMETRY

Collected Date:	Received Date/Time:	Verified Date/Time:
01/18/2016	01/19/2016 17:16:00	01/20/2016 13:38:12

Multiple necrotic cells – chronic inflammation

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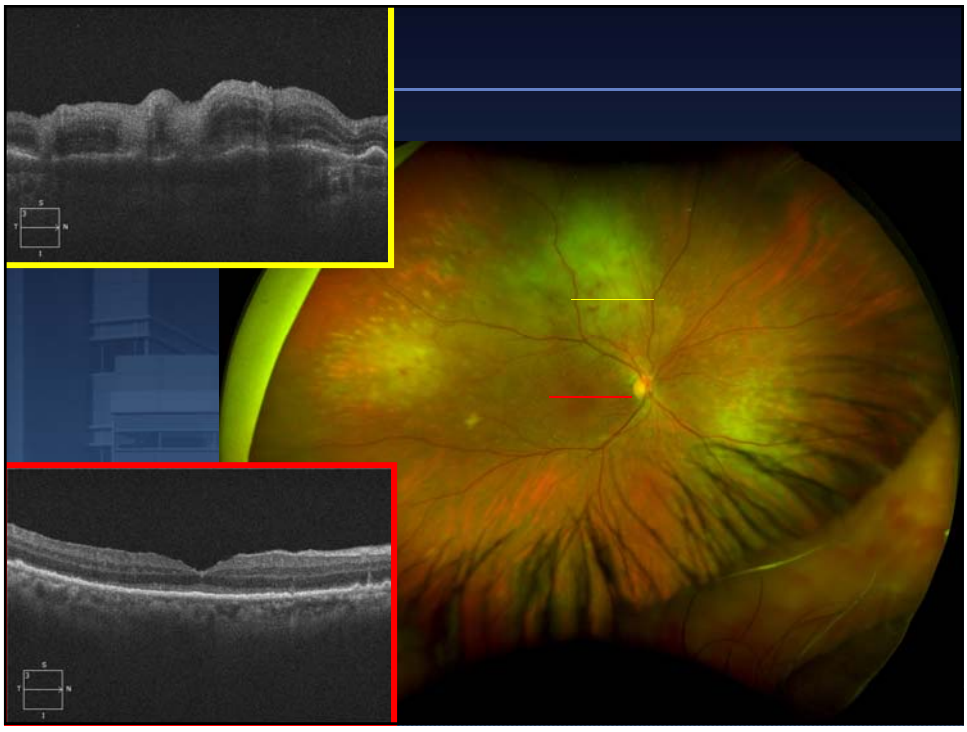

When should a patient start on chronic therapy?

Guidelines

- Active uveitis – treat with high dose of corticosteroids[1]
- Add steroid-sparing agent if inflammation cannot be controlled with <10 mg prednisone within 3 months[1]

1. Jabs DA, et al. *Am J Ophthalmol*. 2000;130:492-513. (A)

So who should get chronic therapy?

- Those who can't taper off prednisone
  - If you have a pt on greater than 10 mg prednisone for greater than 3 months – you need to switch
- Those who have multiple flare ups
  - My rule 3 flare ups within 12 months
- Those who you are controlling with just injections and vision is dropping
  - 20/200 ➔ IVK ➔ 20/25
  - 20/200 ➔ IVK ➔ 20/40
  - 20/400 ➔ IVK ➔ 20/60

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Should I ask my patient to pay for difluprednate?

- Advantages over prednisolone acetate
  - QID therapy as effective as 8x/day pred acetate
  - Fewer pts fail
  - Faster response
- Disadvantages
  - Cost
  - IOP elevation
  - Is the endpoint the same?

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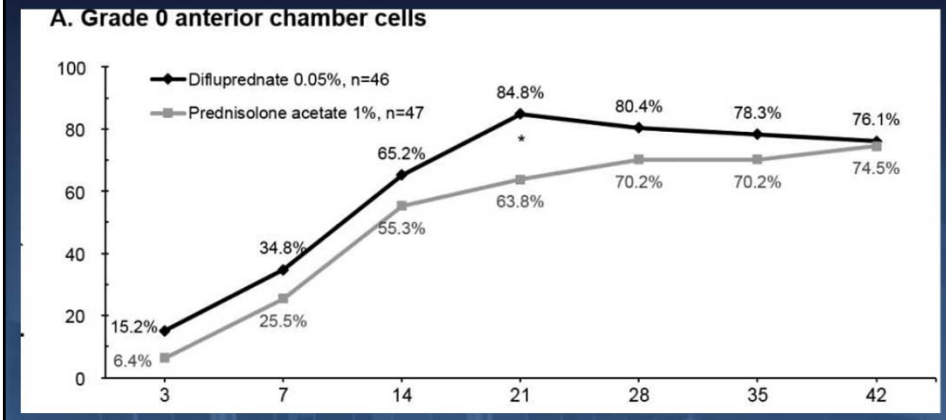
Difluprednate vs. prednisolone acetate



Sheppard J et al IOVS 2014

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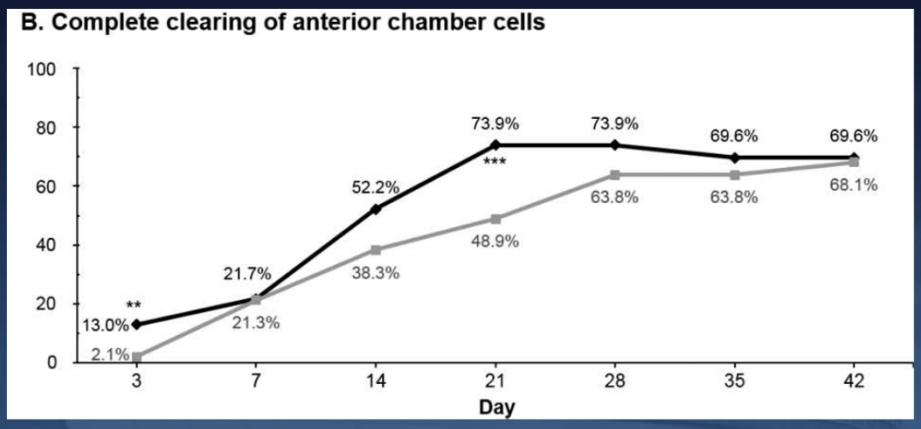
Difluprednate vs. prednisolone acetate



Sheppard J et al IOVS 2014

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So which do I use

- I tend to use Pred acetate based on cost and coverage
- However, I often use difluprednate in those with difficulty with administering drops and/or very active
- Difluprednate has an effect on CME and retinal vascular leakage (Feiler et al 2016)
- Cycloplegia still needs to be used in anterior disease.
- I don't use mild topical steroids

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Dose Escalation

- If the patient does not respond to frequent topical quickly – I escalate therapy to oral steroids
- If I don't think they are using it – I use oral steroids
- If I don't think they are using oral steroids…
- I threaten them with a large bore needle into the eye

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Treatment – Systemic

- Immunosuppressive agents
  - For chronic recurrent disease
  - For severe vision-threatening disease
  - For disease responsive only to high-dose corticosteroids

Jabs DA, et al. *Am J Ophthalmol*. 2000;130:492-513. (A)

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SITE Study

Drug	Success at 1 yr	<= 10 mg Pred	D/C within 1 yr
Mycophenolate	73%	55%	12%
Cyclosporine	51%	36%	10%
Cyclophospamide	76%	61%	33%
Methotrexate	66%	60%	42%
Azathioprine	62%	47%	25%

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Biologic Agents

- Biologic Agents
  - Etanercept (Enbrel) – Anti-TNF
  - Infliximab (Remicade) – Anti-TNF
  - Adalimumab (Humira) – Anti- TNF
- Some reports of excellent response
- Now my second line agent (first line for some disease)
- Long term complications?
- Cost

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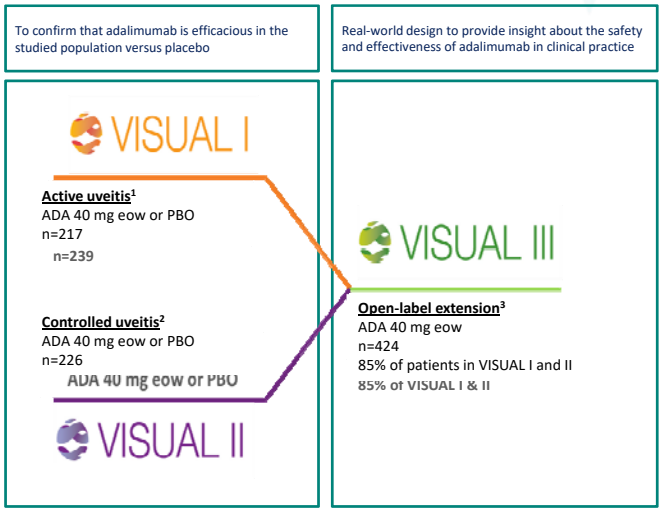
RCTs in Non-infectious Uveitis: the VISUAL Program

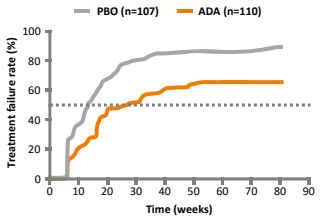


ADA, adalimumab; eow, every other week; PBO, placebo

1. Jaffe G, et al. N Engl J Med 2016;375:932–943;
2. Nguyen QD, et al. Lancet 2016;pii: S0140-6736(16)31339–3 [Epub ahead of print];
3. Suhler EB, et al. Presented at the 9th International Symposium on Uveitis. 21 August 2016, Dublin, Ireland

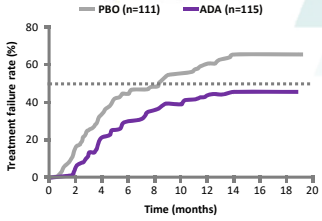
Early and Sustained Effect of Adalimumab on the Rate of Treatment Failure Compared with Placebo

VISUAL I



	PBO	ADA
Median time to treatment failure	13 weeks	24 weeks
HR; p-value	0.50; p<0.001	
95% CI for HR	(0.36–0.70)	

VISUAL II



	PBO	ADA
Median time to treatment failure	8.3 months	>18 months
HR; p-value	0.57; p=0.004	
95% CI for HR	(0.39–0.84)	

- The risk of failing treatment (flare or vision loss) was reduced by almost half and the time to treatment failure was approximately doubled

CI, confidence interval; HR, hazard ratio

1. Jaffe G, et al. N Engl J Med 2016;375:932–943;
2. Nguyen QD, et al. Lancet 2016;pii: S0140-6736(16)31339–3 [Epub ahead of print]

Treatment – Local Therapy

- Perioculars
- Intravitreal steroids
  - Triamcinolone
- Sustained-delivery devices
  - Fluocinolone acetonide implant
  - Dexamethasone intravitreal implant
- I use local injections as bridge therapy, for acute flares in chronic patients, for CME.
- If they need chronic therapy – fluocinolone implant or systemic

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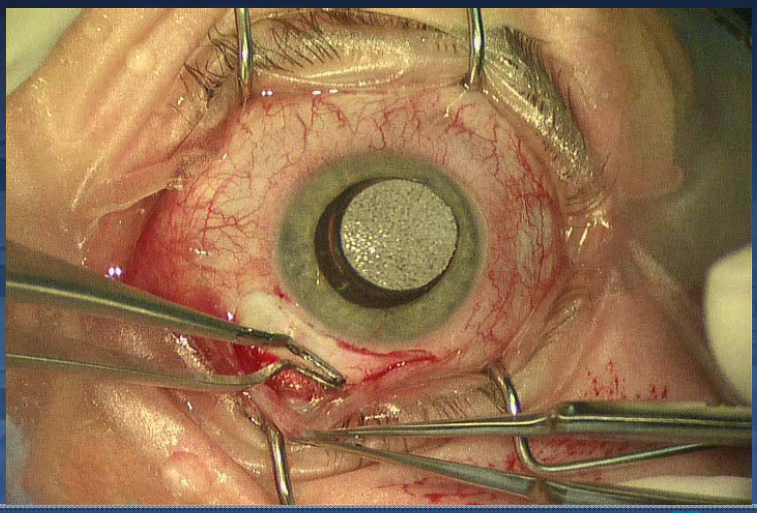
Fluocinolone Acetonide Implant



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Clinical Trial Results

- Reduction in ocular inflammatory episodes
  - Average time to recurrence – 30-36 months
- Need for additional therapy
  - Systemic immunosuppression rates dropped from 44% to 8% at Year 3
- 100% cataract rate
- 70% IOP spike within 12 months, 40% glaucoma surgery rate

Callahan DG, et al. *Arch Ophthalmol*. 2008;126:1191-1201. (B)

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Sustained Local Therapy

- Patients who are good candidates
  - Recurrent posterior/intermediate uveitis
  - Ocular disease only
  - Recurrent cystoid macular edema
  - No previous history of glaucoma
  - “Pseudophakic with glaucoma tubes”

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Sustained Local Therapy

- Patients who are good candidates
  - Recurrent posterior/intermediate uveitis
  - Ocular disease only
  - **Recurrent cystoid macular edema**
  - No previous history of glaucoma
  - “Pseudophakic with glaucoma tubes”

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MUST Trial

- Multicenter Uveitis Steroid Treatment Trial
- Patients with active uveitis randomized to oral prednisone with systemic immunosuppressive agents vs. fluocinolone acetonide implantation
- Similar outcomes at year 2 between both groups
- Similar outcomes at year 5 between both groups

Multicenter Uveitis Steroid Treatment Trial Research Group. *Am J Ophthalmol*. 2010;149:550-561.

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When can we safely perform cataract surgery?

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Case Presentation

- The optometrist who never refers you a patient sends you a patient!
- All of those holiday baskets finally have paid off!
- “Its an easy one”
- “I think they will need cataract surgery soon”
- “You’re welcome”

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Case Presentation

- 48 year old male
- Can’t work now
- Uninsured
- Brother is a malpractice attorney
- Close cousin of your former long term girlfriend/boyfriend who broke up with you because “you were not serious enough”

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HPI

- 48 Year Old Male
- Hx of scleritis
- Has been on infliximab x 2 years in past – then stopped and failed mycophenoloate
- Was on Adalimumab x 6 months
- MTX 25mg weekly
- On and off PO steroids, usually 20mg but goes up to 40mg when flares
- Current meds → on Pred 20mg

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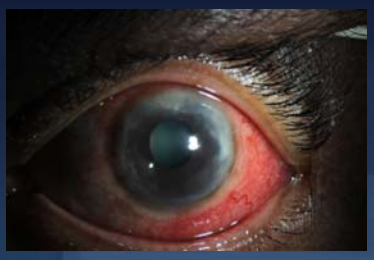
Initial Visit



- Vision 20/40 OD, 20/125 OS

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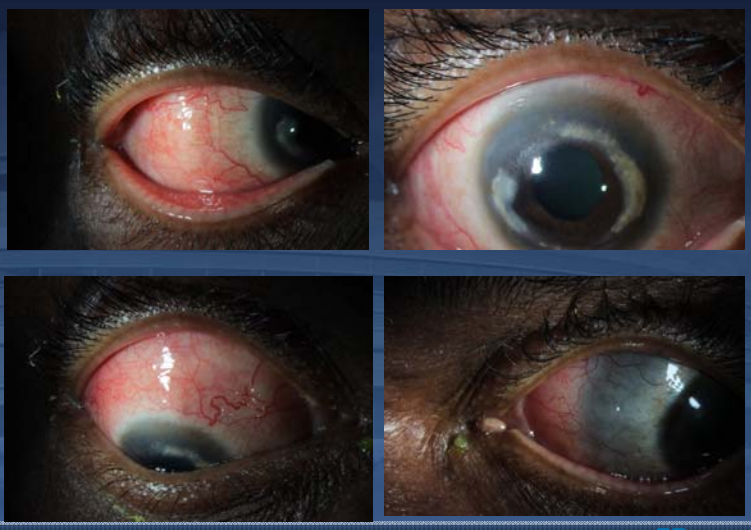
4 months later

- Vision 20/80 OD, 20/500 OS



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Plan

- Start Cyclosporin
- Increase prednisone 40mg

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Follow Up

- Becomes inactive x 3 months
- Visually significant cataracts OU
- Vision 20/200 OU

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Cataract Surgery OS

- Complex with bag rupture and vitreous loss
- Vitreous to wound
- Send to Sunil…..

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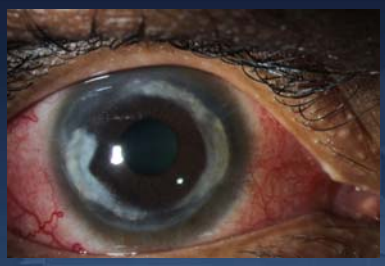
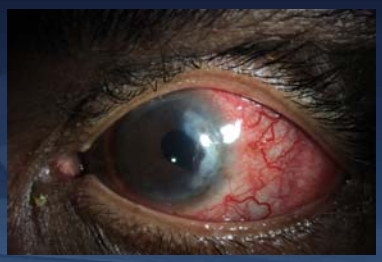
1 Month Post-Op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What To Do Now?

- Inflammation now significantly worse
- What should we do team?
- My plan:
- Send to Angela….
- Admit for 3 days IV Solumedrol
- Also started on IV cytoxan
- After 3 days Solumedrol placed on Prednisone 60mg

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Exam 2 Weeks Later



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It Took Angela and I A Long Time….

- Cyclophosphamide
- Steroids
- Adalimumab
- Cyclophosphamide again
- Infliximab 10 mg/kg monthly
- 1 year later off of all steroids
- Now…

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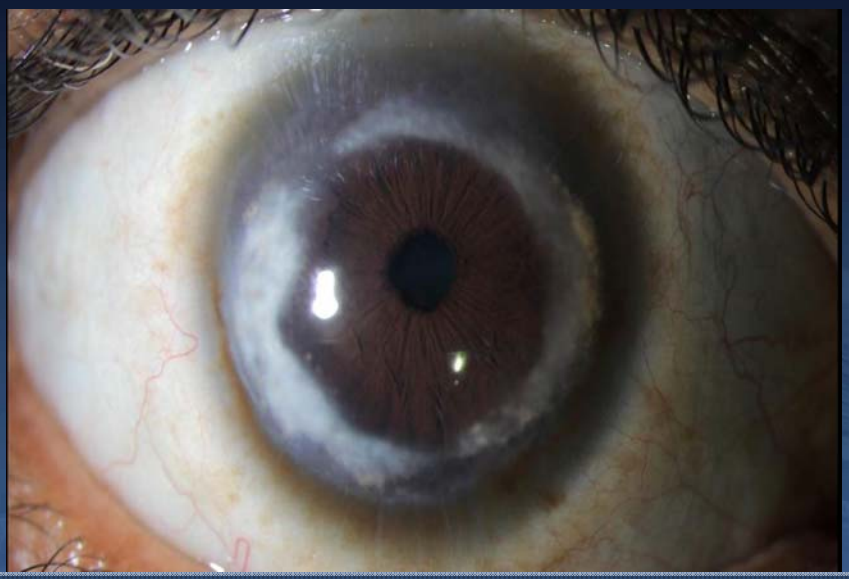
Cataract OD



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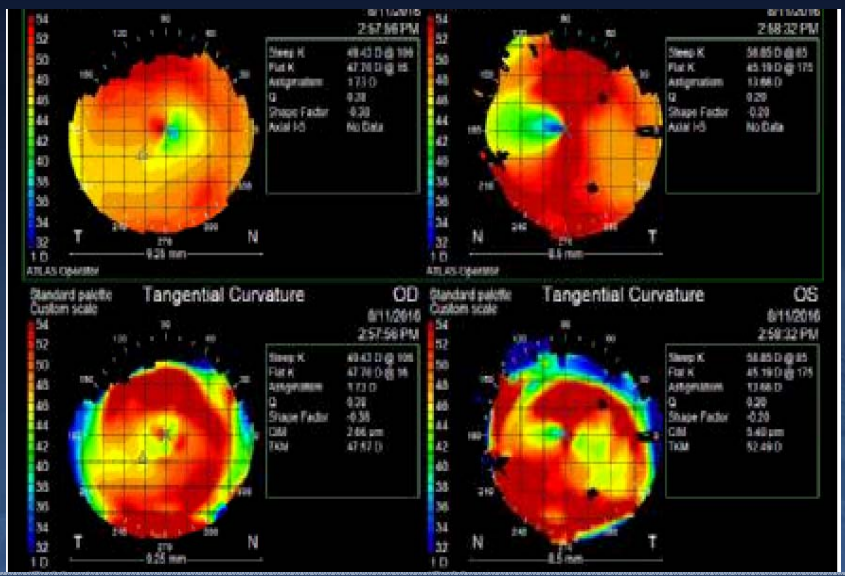

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When is okay to do surgery?

- Historically
- Wait for 3 months of inactivity
- Multiple papers report improved outcomes
- Is it because:
  - Peri-op management
  - Better phaco surgery
  - Better IOLs

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Now

- 3 months of quiescence desirable
- But, we operate when there is minimal activity and uveitis is controlled
- Operate during the window of opportunity
- Aggressive peri-op management

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Perioperative management?

- Why?
- Reduce complication risk
  - Recurrence (as high 53%)
  - Post-operative fibrin formation (up to 30%)
  - CME (5-40%)
  - IOL deposition (10-20%)
  - PCO? (50-90%)

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Classic regimen

Uveitis Type	Maintenance Regimen	Peri-op Regimen
Inactive anterior uveitis	None	None
Chronic Anterior Uveitis	Topical Steroids	Pred drops 6x/day 1 week prior +/- po steroids 30-60 mg
Chronic Panuveitis - Controlled	Immunosuppressive +/- Topical +/- Prednisone	Pred drops 6x/day + PO steroids (at least 30 mg)
Chronic Panuveitis Uncontrolled	Immunosuppressive +/- Topical +/- prednisone	Pred Drops q1-2 hour + high dose po steroid

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My Perioperative Approach

- In quiet eyes with no history of recent inflammation – preop topicals
- In chronic anterior uveitis – Preop topicals + 1 week prior dexamethasone implant vs intraop triamcinolone vs po steroids
- In posterior disease – combination of topical, intravitreal and po steroids.
- If I am not sure if there is an infectious cause – I DO NOT INJECT STEROIDS
- Scleritis patients - I avoid intravitreal injections, I use po steroids +/- periocular steroids.
- Taper slowly topicals and po.

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Classic regimen Plus Intravitreal

Uveitis Type	Maintenance Regimen	Peri-op Regimen
Inactive anterior uveitis	None	**Topicals +/- IVT or dex 1 week prior**
Chronic Anterior Uveitis	Topical Steroids	Pred drops 6x/day 1 week prior +/- po steroids 30-60 mg or **IVT or dex 1 week prior**
Chronic Panuveitis - Controlled	Immunosuppressive +/- Topical +/- Prednisone	Pred drops 6x/day +/- PO steroids (at least 30 mg) **or IVT or dex 1 week**
Chronic Panuveitis Uncontrolled	Immunosuppressive +/- Topical +/- prednisone	Pred Drops q1-2 hour + high dose po steroid + **IVT or dex 1 week prior**

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What's My Surgical Technique for CE/IOL?

- I am a retina surgeon who has healthy relationships with my anterior segment colleagues so I stay away from cataract surgery
- In general
  - Control of iris – try to minimize iris manipulation if possible. Iris hooks and Malyugian rings are used often in our institute for post synechaie
  - Stain capsule
  - Acrylic IOLs
  - I do not recommend prophylactic vitrectomy/posterior capsulectomy for adults

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Scleritis and cataract

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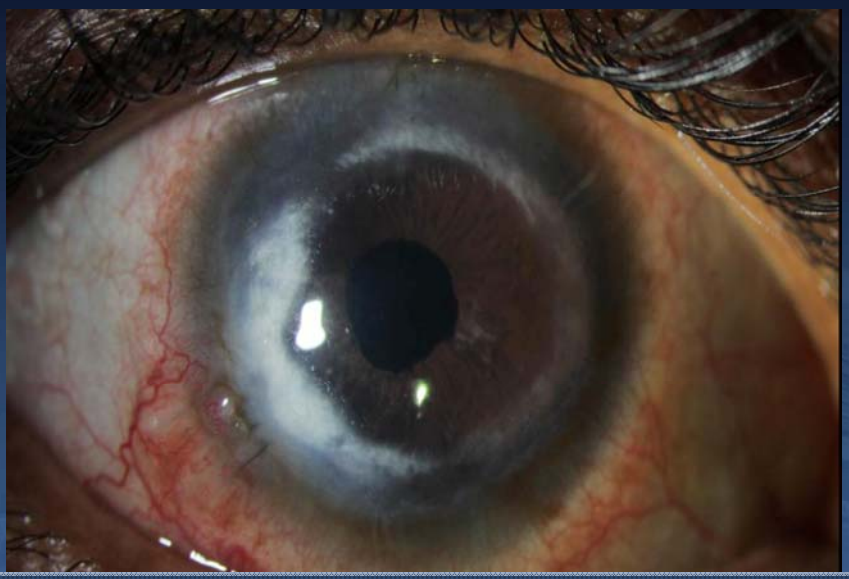
Postop Pic



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Back to our original patient

- Heavy topical therapy pre-op
- Unable to get ozurdex approval
- Intravitreal triamcinolone at time of surgery
- PO steroids 5 days prior
- Does great
- 20/30 1 year out
- No postop inflammation
- Kept on topicals x 3 months….

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What about post-op inflammation?

- Most chronic post-op CE/IOL inflammation is not uveitis
- Most is due to surgery and genetics
- Not enough topical therapy or not for long enough
- Also your cataract surgery wasn't perfect (its okay I wont tell anyone)
- But some can be concerning and warrant work-ups
- So first – increase topical therapy frequency (real topical steroids)
- Then if not quiet – add po steroids – if not better - refer

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Post surgery inflammation

- Consider
  - Infection
  - IOL touch of iris
  - Was there intraoperative manipulation of iris
- Tissue sample
  - Vitreous or anterior chamber tap/inject
  - IOL removal/PPV

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Case Presentation

- CC: Recurrent uveitis, Left Eye
- HPI: 62 year-old man
  - Presented with redness, blurred vision OS one month ago
  - Improved with drops but 2 recurrences on taper, last one 10 days ago
- Past Ocular Hx:
  - CE OS 1 year ago, OD 10 months ago
  - Amblyopia OS

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Exam

- OD 20/30 OS 20/70
- SLE
  - OD: Quiet
  - OS: 2-3 + AC cell, Mutton Fat KP, PCIOL, 2+ Vit Cell and 2+ Haze

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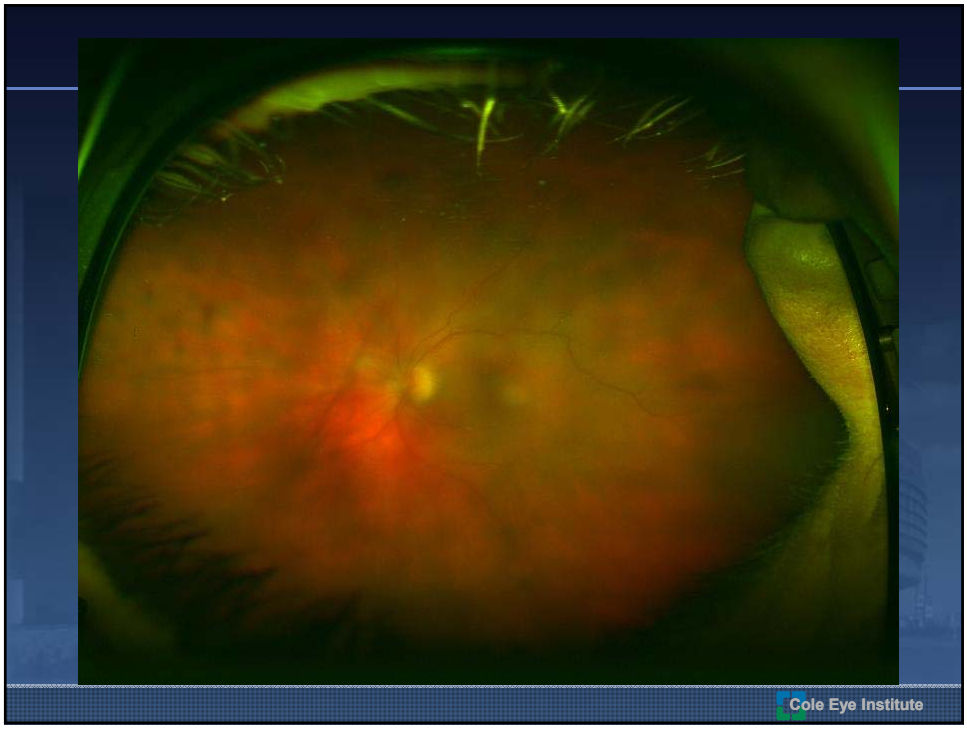
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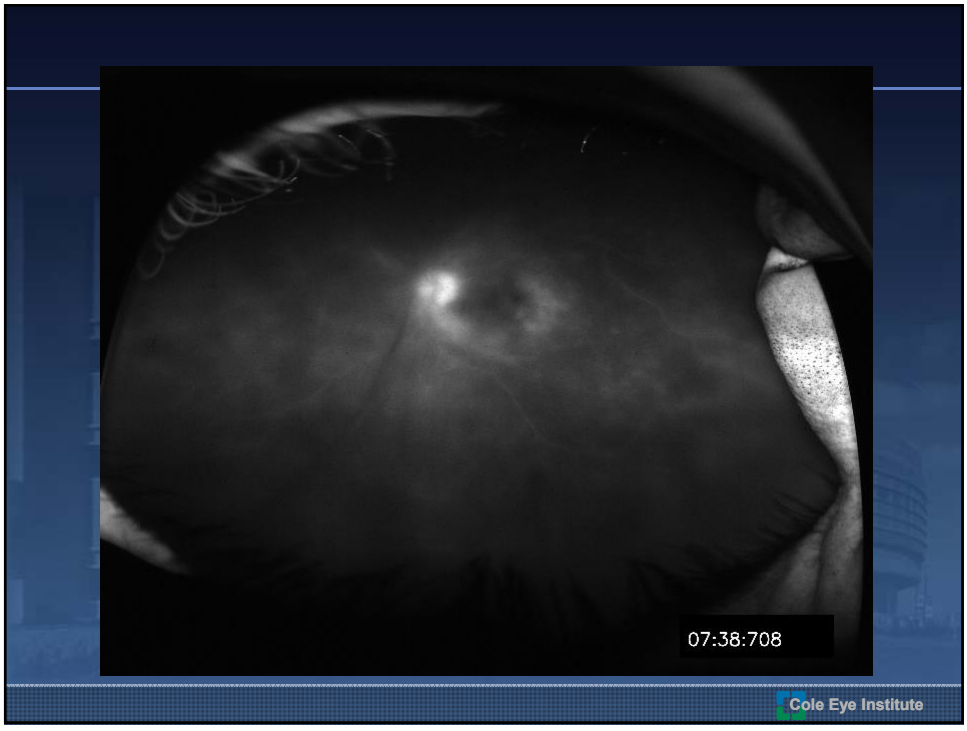
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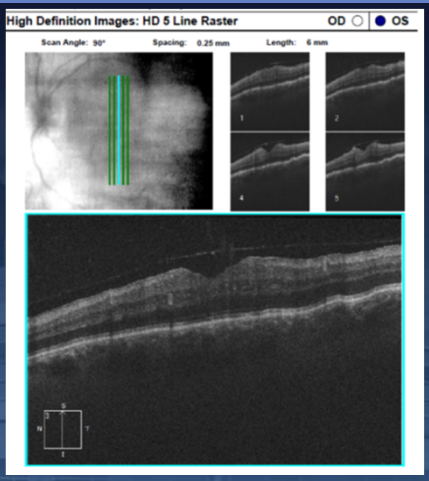

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Assessment

- Unilateral Panuveitis, Left Eye
- Two episodes in past 6 weeks
- Started 1 year after phaco – related to cataract surgery?
- Plan
- Labs

  CBC, CMP, ACE, HLA-B27, Syphilis IgG, quantiferon
- Start Difluprednate, po steroids

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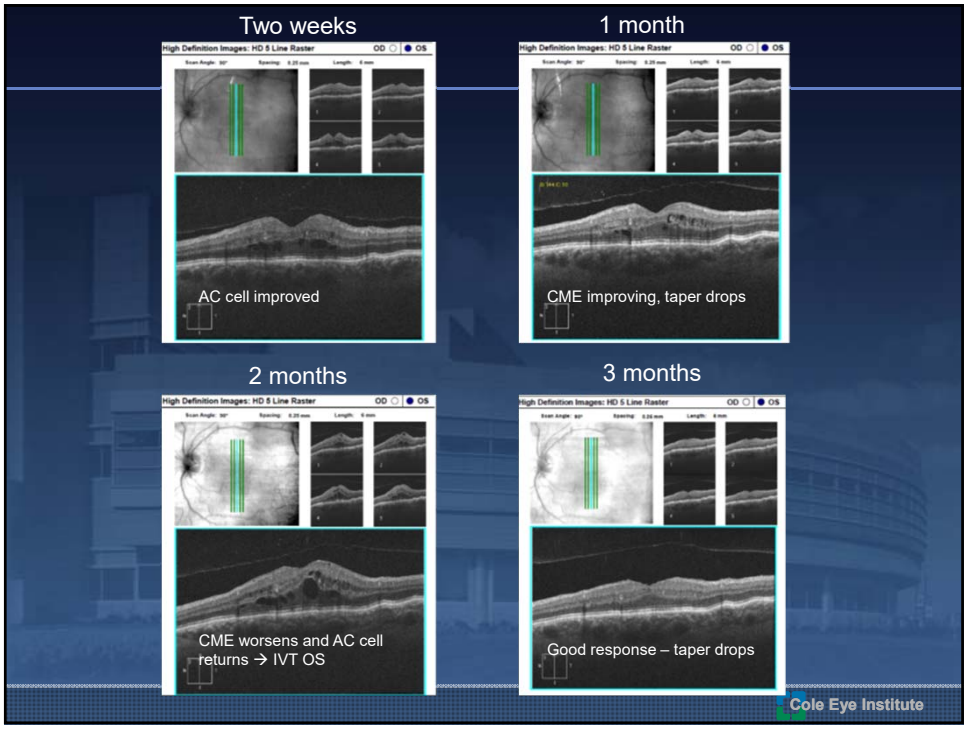

Case Presentation

- Increasing anterior chamber cell over next few visits despite topicals
- Plan?
- Another injection?
- Restart oral prednisone?

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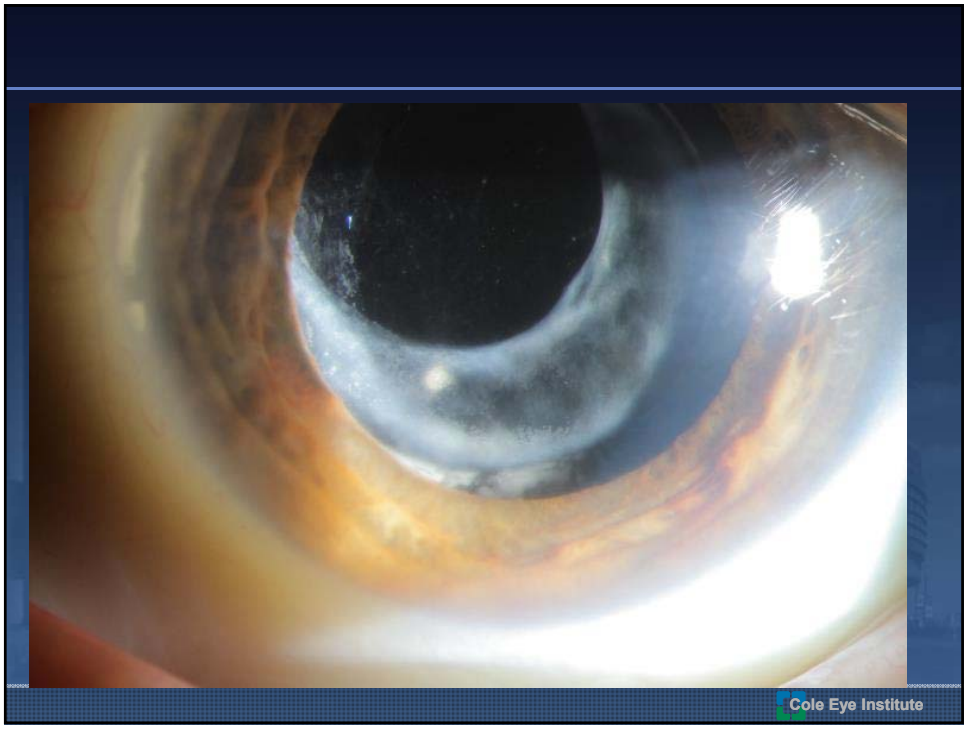
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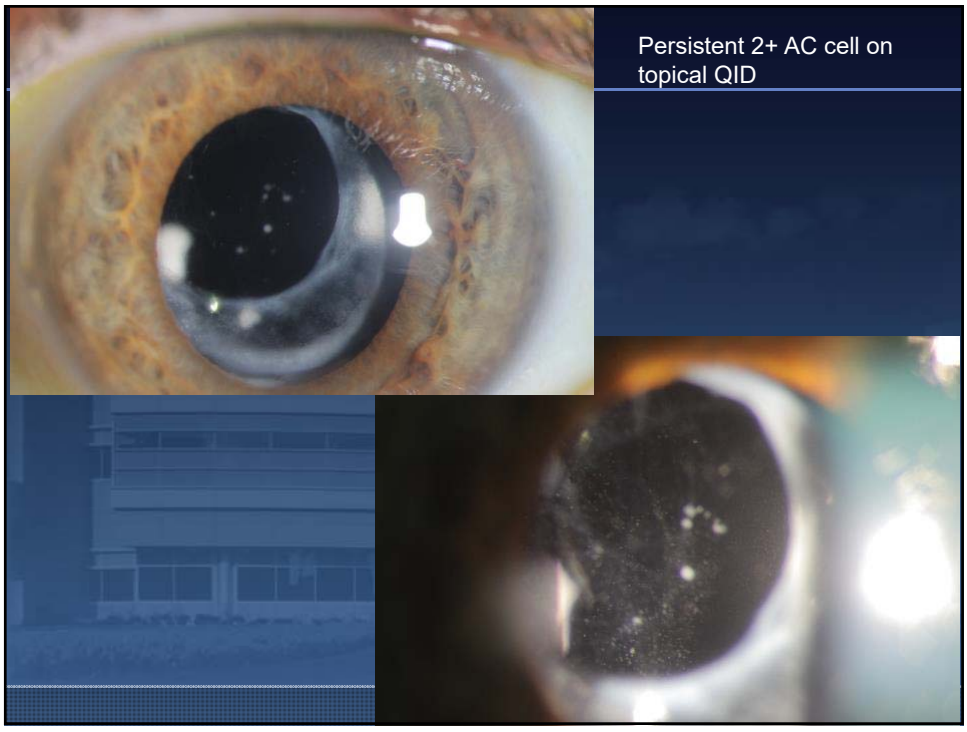
Persistent 2+ AC cell on topical QID

Assessment

- Chronic endophthalmitis
- AC tap – P. acnes
- What now?
- Inject vs IOL explant?
- Receives injection of vancomycin with plan for PPV/explant

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Surgical Video

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What signs should I worry about?

- When things don't respond they way I expect
  - High dose prednisone should quiet most inflammatory diseases
  - Retinal whitening that appears out of nowhere
  - Infections that progress on therapy
- Necrosis of the retinal, scleral melts
- Diffuse hemorrhage and diffuse vascular sheathing
- Anyone referred to me with worsening vision after intravitreal/periocular steroids
- Hypopyon that I can't explain

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Last Case

- Let's put it all together
- And show you
- Why ophthalmology is awesome….

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Case Presentation

- 32 year old male
- Transferred from outside hospital for ophthalmology intervention
- 3 week history of progressive painful swallowing, diagnosed with candida esophagitis
- Unable to eat – losing weight, on TPN
- While on TPN – develops sudden floaters and vision loss
- Diagnosed with candida endophthalmitis
- Anti-fungals changed, but progressive worsening of vision
- Transferred – ophtho resident called

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- Vision 20/200 OD 20/20 OS
- Tr AC cell
- DFE: see photos
- But first – I will show you his mouth

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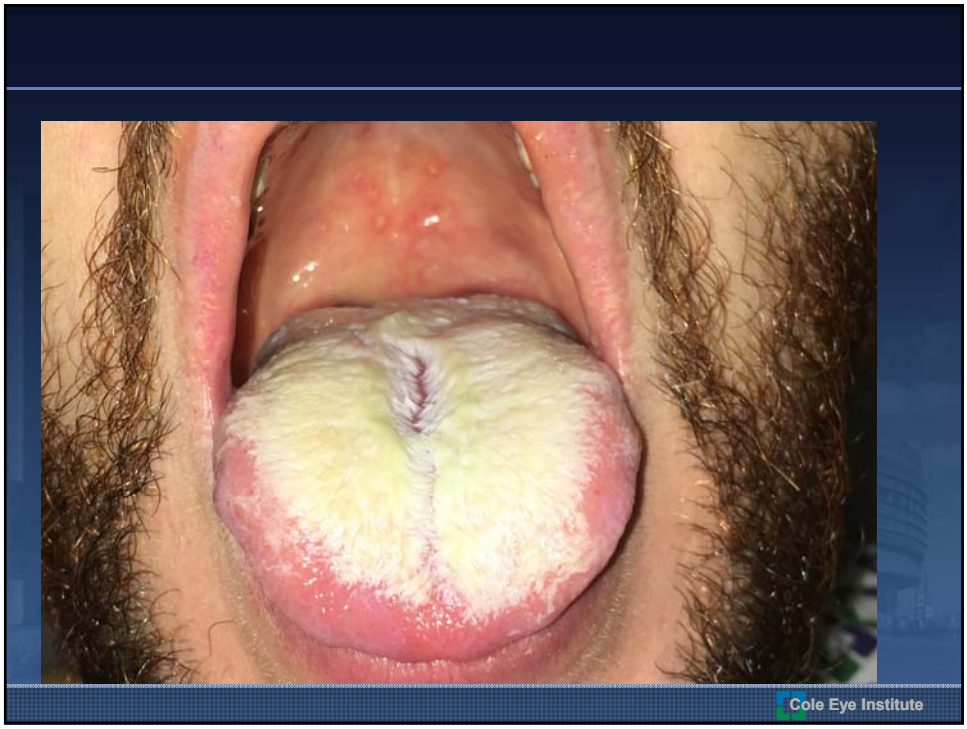
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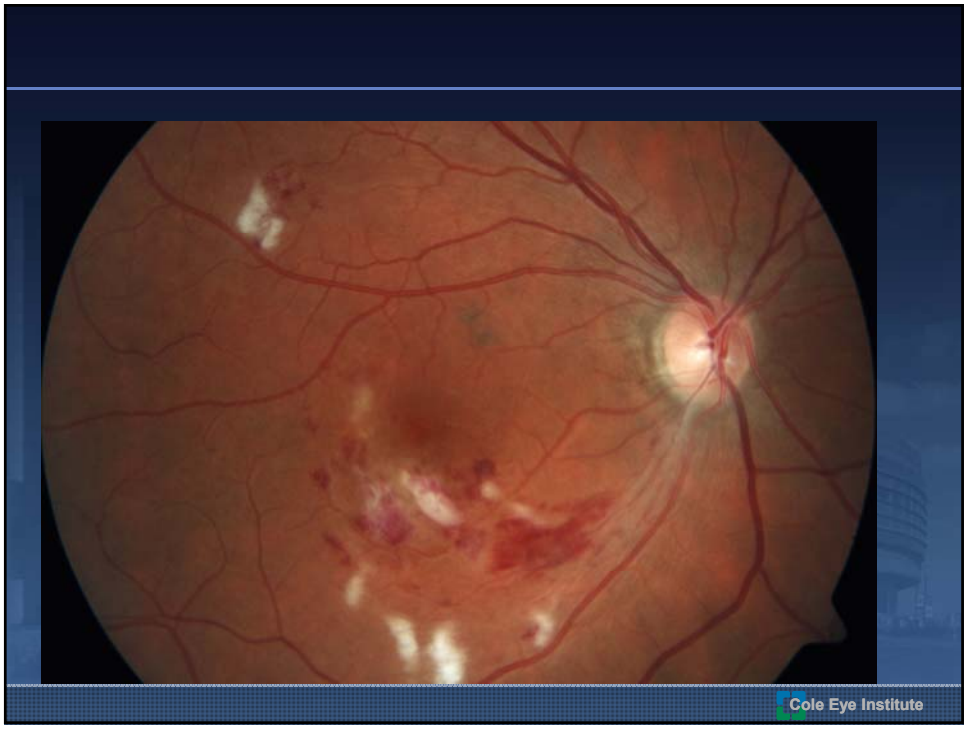
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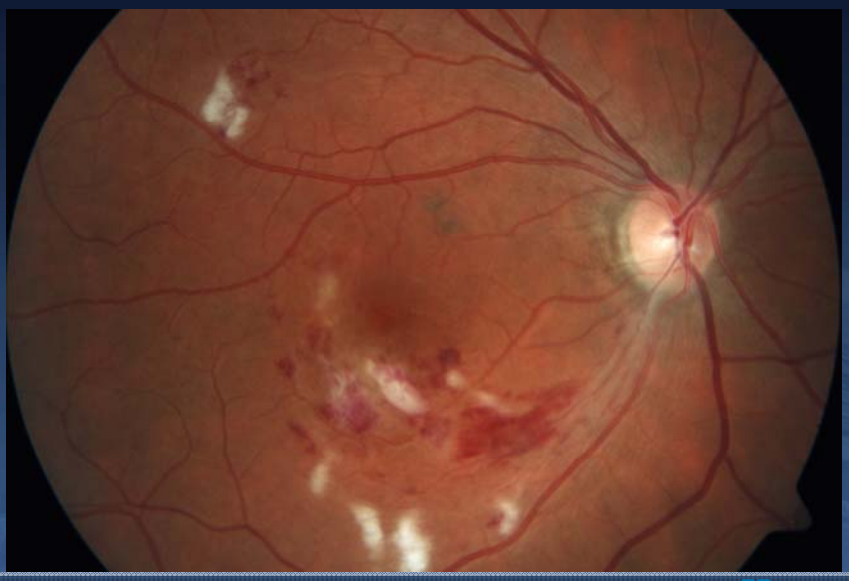
So my resident thinks……

- This does not make sense
- What would Sunil do?
- Recheck everything…



Resident thinking…

- Multiple ischemic areas
- Looks like artery occlusions
- Can systemic fungal infection give you artery occlusion?
- Maybe but rare, and no lesions OS, and no full thickness lesions
- But inflammatory disease can.
- Let me look at his mouth again

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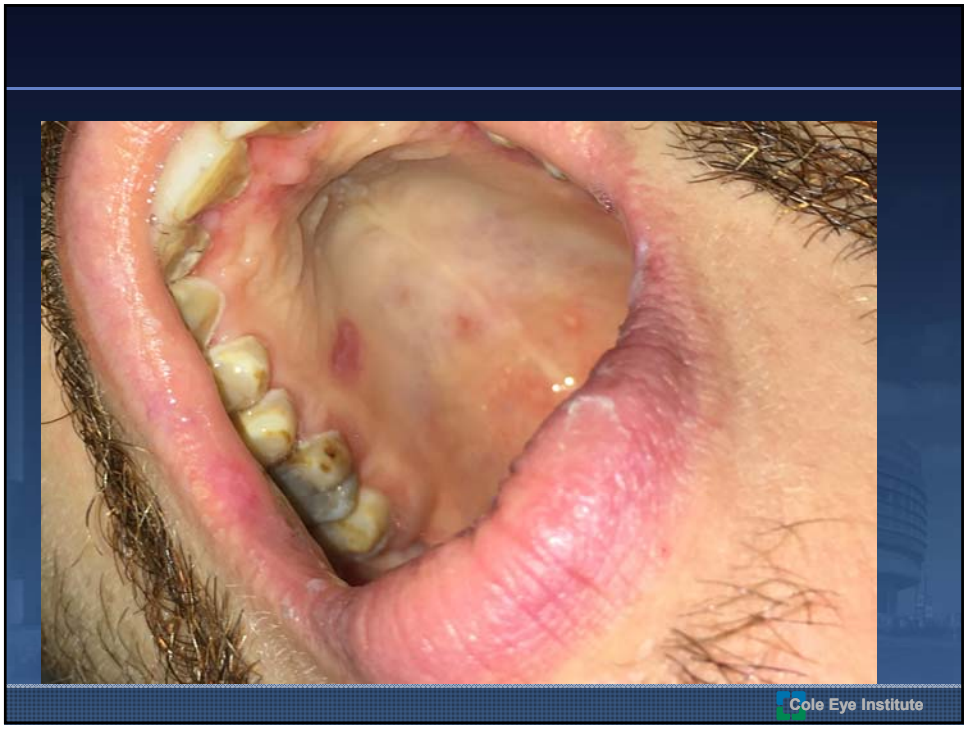
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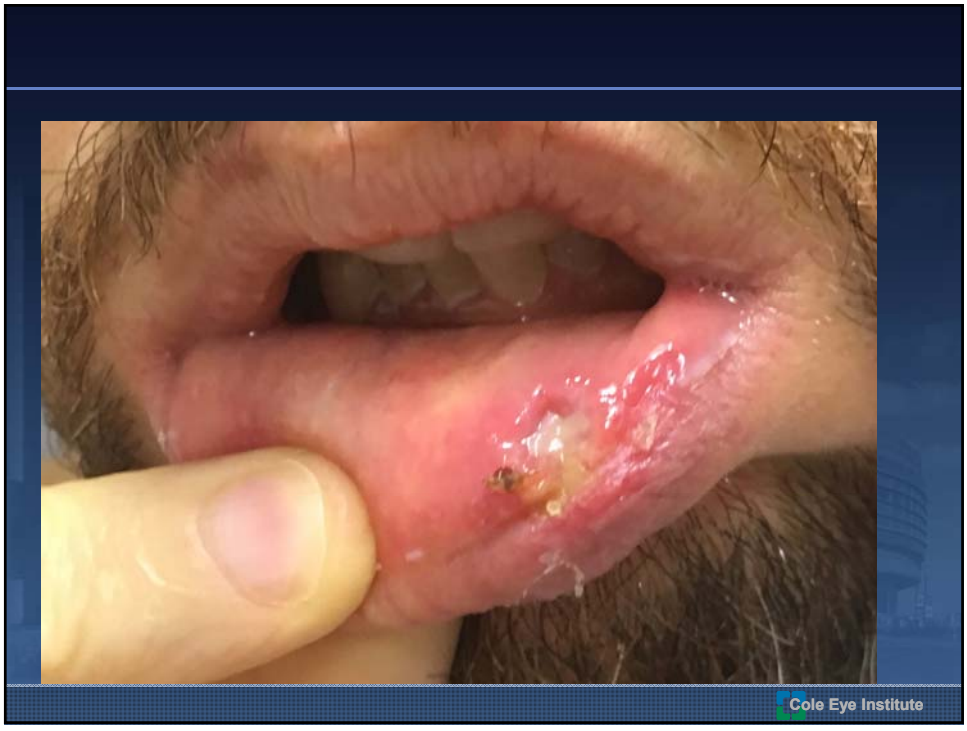
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So…

- Mouth ulcer, multiple artery occlusions
- ?Behcet's
- What else should he have?
- Yup – lets check you everywhere

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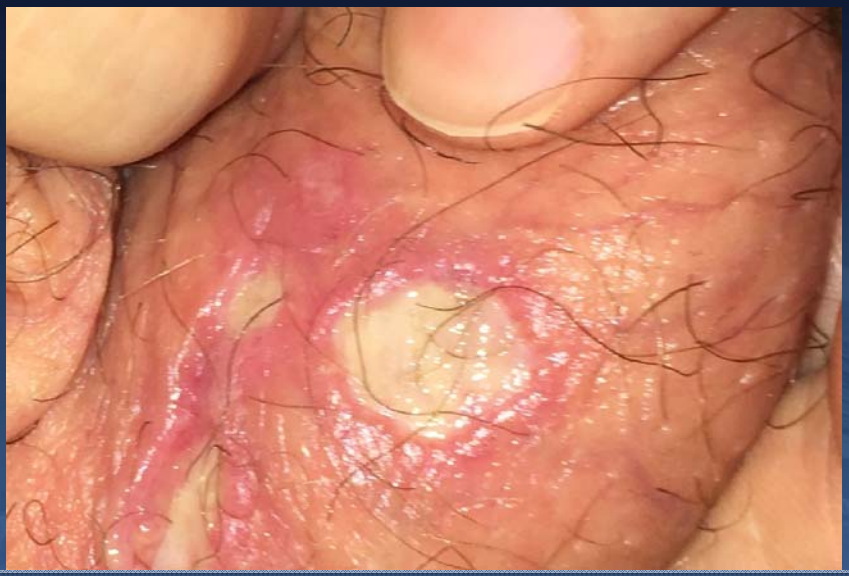

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Success!

- Oral ulcers, genital ulcers, retinitis = Behcet's

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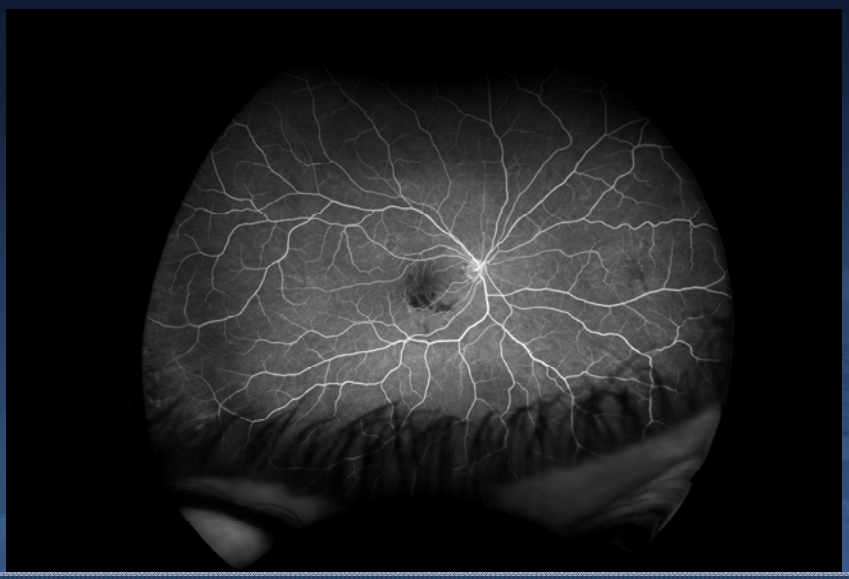

Case Presentation

- Started on IV Solumedrol
- Eating in 2 days
- Esophagus lesions determined to be ulcers – resolved within 5 days
- Gains weight back
- Started on IV infliximab
- f/u vision 20/30 OD, 20/20 OS
- Ophtho resident – saves this patient's life.

Lessons learned

- Take the outside history with a grain of salt
- If clinical picture does not fit – re-examine diagnosis
- Sometimes the eye exam needs to be done without your clothes off.

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Summary

- We have answered some questions
- When to work-up and how to work up a patient
- Treat patients with chronic therapy when they display chronic disease
- Periop management/ Post-op inflammation management
- Watch out for the bad signs
- Be observant and constantly question the supposed “truth”
- Just in case: srivass2@ccf.org

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