Uveitis Update 2023
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Uve	itis Update 2023 – no it wasn't /ID or your vaccine that caused
COV	r uveitis
your	uveius
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	Programs
	Cole Eye Institute, Cleveland Clinic
	Cole Eve Institute Cleveland Clinic

Consultant/Advisory Board: Bausch and Lomb, Allergan, Clearside, Eyepoint, Regeneron, Santen, Sanofi, Zeiss, Optos, Novartis Research Grants: Bausch and Lomb, Allergan, Novartis, Clearside, Zeiss, Sanofi, Santen Licensing Royalty: Bioptigen, Synergetics

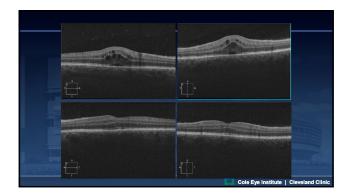
This is my 1st time at this meeting, but I have done a number of ophthalmology society talks.... • The reviews are usually bad.... • "Ophthalmology is sunny and beautiful like Florida and uveitis is dark and dreary.... like Cleveland." • "I am disappointed that the uveitis lecture did not include a wet lab on premium IOLs in uveitis patients" But every once in a while.... • "The uveitis speaker talked so fast that I didn't mind it was about uveitis & he told a couple of STDs jokes....bring him back!" Cole Eye Institute | Cleveland Clinic Goals Today • A couple of cases to help you think through what to do How to decide what to order • What kind of meds to use to treat chronic uveitis • How to help yourself, figure what you are comfortable with and when to refer. Will show you a real COVID uveitis case! And why ophthalmology is awesome..... Cole Eye Institute | Cleveland Cli What's the point of the work-up? • Recognize that uveitis can be a local manifestation of a systemic problem • Uveitis can also be a local issue (trauma, infection) without a systemic issue • The goal of a work-up is to: Identify a cause that would allow to treat specifically and avoid complications Rule out infections (malignancies) allowing the use of immune suppressive medications Cole Eye Institute | Cleveland Clinic

A proper work-up Requires a pretty good clinical exam Identifying all areas of activity Helps with differential But also assessing risk of vision loss Clinical History is vital Targeted ROS Processing all this information together Treating the patient Don't forget - 50-60% of uveitis is idiopathic Cole Eye Institute | Cleveland Clinic

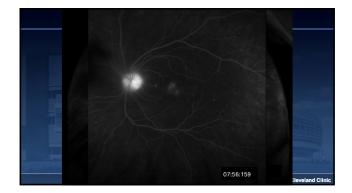
44 yo M presents with 3 week history of blurry vision and light sensitivity in both eyes Started on prednisolone q1h and atropine BID in both eyes by outside ophthalmologist Diagnosed with psoriasis and on etanercept Has an unclear history of previous Tb test

Exam	
• OD 20/70, OS 20/40	
SLE Post synechiae OU, quiet AC	
• 1-2+ vit cell OU	
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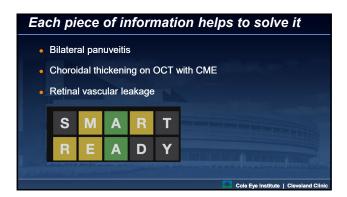












Differential Bilateral panuveitis with CME Psoriasis-associated (HLA-B27) Tuberculosis Medication-induced (Enbrel) Sarcoidosis What else do you want to know?

Tailor your ROS to the disease process
Tuberculosis – travel history, prison, work in medical field?
Psoriasis – scaling skin changes, arthritic issues?
 Enbrel associated uveitis – new skin changes, new inflammatory symptoms
 Sarcoidosis – Pulmonary symptoms, Skin changes.
Syphilis – review of risk factors
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So I wasn't bashful and I ask	ed					
Any new skin changes?	S	М	Α	R	Т	
 My tattoos look different. 	R	Е	Α	D	Υ	
• Would you like to see my tattoos?	С	R	Α	M	E	
Ummmwhere is it exactly?						
Starts to undress						
Please page the retina fellow						
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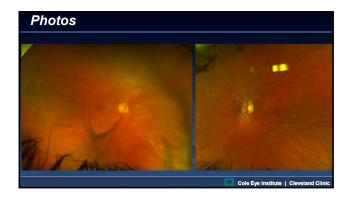


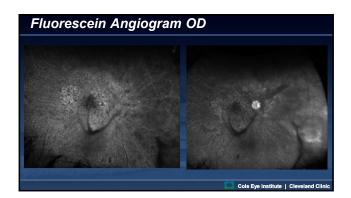


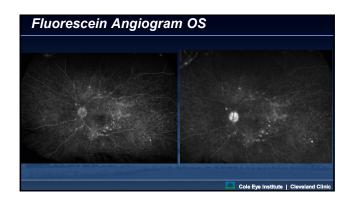
Case Presentation

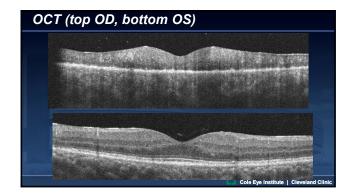
- Labs: ACE, CBC/CMP, syphilis IgG, HLA-B27, quant gold, CXR - negative
- When suspicious for sarcoidosis, I will order a CT chest
- Positive for Hilar adenopathy biopsy positive for sarcoidosis
- No longer with dx of psoriatic arthritis, on prednisone, switched off etanercept to another agent.
- Dx of sarcoidosis I used his images and because I looked at his tattoos.....
 S A R C O I D

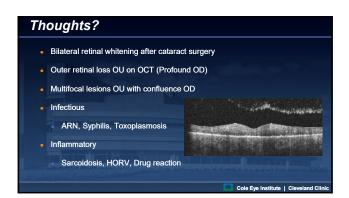
The power of ROS • Use your imaging to guide you. • Not asking you to ask the 150 questions you did as a medical student • Focus depending on presentation: • Older patient - new medications, recent illness, hospitalization, systemic cancers. Younger patients – skin changes, arthritic changes, lung disease, history of STDs, drug use Cole Eye Institute | Cleveland Clinic **Case Presentation** • 49 year old male presents for vision loss after dropless cataract surgery OU • Presented with a few weeks history with vision loss noted to have cataract 6 weeks ago had ce/iol "dropless" intravitreal steroids used OS. Did well then 4 weeks ago similar surgery OD. Noted significant decline in vision at postop week 1. • I'll admit I didn't ask if he had femto or a multifocal placed. Cole Eye Institute | Cleveland Clinic Case Presentation • CF OD 20/25 OS • 1+ cell OU • Triamcinolone scattered in vitreous OU



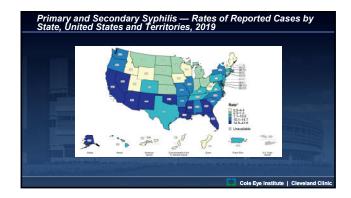


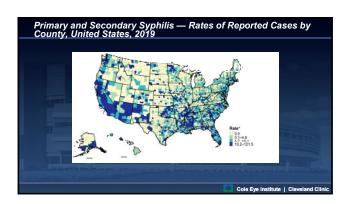






Syphilis IgG positive, RPR 1:32
Called patient to discuss results
"How did I get syphilis?"
Referred patient to Abbas Haider, MD, world renowned expert in spontaneous spirochete infections

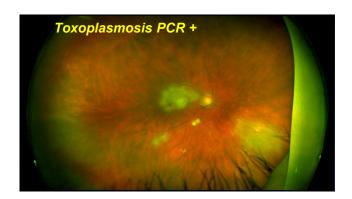




Not looking (vision loss in a 49 year old) Not thinking or taking the easy way out (all vision loss = cataracts) Not testing or letting a test dictate treatment when everything else doesn't make sense Local steroids in infectious cases Not looking prior to delivering a long acting steroid in a situation where its probably not needed

In order to figure it out you need to ask it.... Ask the uncomfortable questions: IVDA? Sexual activity? Ulcers? You voted for whom? Are you vaccinated? Why not?

l w	ish it was just one case
	60 year old male
•	Followed for a lesion for years per him OD
	Worsening vision OD
	Noted to have a cataract
	Rapid vision loss after dropless cataract surgery
	HM vision
	Calls Employable 1 Clausters Office







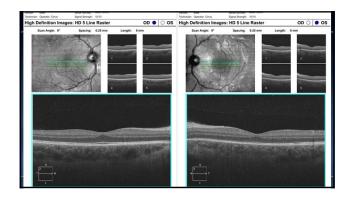
Take home message

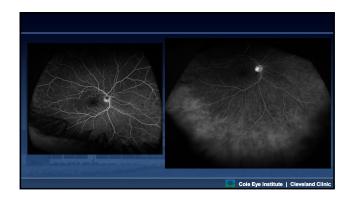
- You have to look in the eye, You have to think about why patient is not seeing
- Clear lens will not lead to 20/500 vision in a 40 year old.
- Ask why prior to putting a long acting steroid in the eye
- If you need steroids for uveitis, start with po steroids, If responds, then consider local injection
- If worsening or not responding reconsider diagnosis
- Mandates close follow-up after beginning steroids

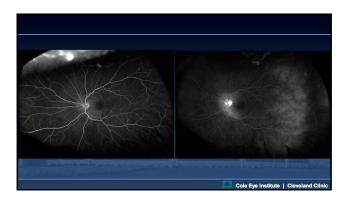
What should I order? Think about your population and your patient (ROS) Recurrent anterior uveitis I consider: Syphilis IgG, Quantiferon Gold, ACE, CXR HLA B27 in unilateral anterior, Urine B-2 microglobulin for acute bilateral disease esp kids ANA, RF in kids with JIA Consider AC tap for viral PCR For posterior/panuveitis Toxo, Bartonella depending on the presentation, HLA-A29 - birdshot, Chest CT if suspicious for sarcoidosis Retinal vasculitis – warrants a complete work-up for systemic vasculitis Tissue biopsy in elderly

To reduce the mistakes – image properly Where do I think the inflammation is and is there an imaging test that highlights that area better? Can I use this test as an outcome measure to follow patients – i.e. will it improve on steroids or antivirals or antibiotics etc. Widefield photo when I can't see the retina (Small pupils, kids or if you don't look in the back of the eye often and uncomfortable with your exam) OCT for almost everyone (OCTA – maybe for CNVM) Angiography for intermediate, posterior or panuveitis, ICG for choroidal disease, Autofluorescence for posterior uveitis (flashes) U/S for posterior/choroidal disease

OCT as baseline diagnostic test for uveitis APMPPE VKH Sarcoidosis Syphilis Cale Be Institute | Cleveland Clinic







Uveitis Secondary to Medications • Topiramate - Anterior Uveitis (AU), choroidals, effusion • Bisphosphonates – AU, episcleritis/scleritis • Cidofovir – hypotony, panuveitis, fibrin • Etanercept – secondary sarcoidosis • Oral Moxifloxacin - pigment dispersion, AU • Topical therapy – brimonidine, etc • Checkpoint inhibitors – VKH like inflammation, AU BRAF/MEK inhibitors – choroidals/CSR like changes Vaccines – Zostavax, HPV, in theory any including COVID-19 Intravitreal therapy – brolucizumab, other anti-VEGF Treatment for uveitis in 2023 • For acute disease • Topical – prednisolone acetate and difluprednate Systemic – oral prednisone (0.5 mg – 1 mg/kg, max 80) • First time acute presentation oral and topical should be first line, injection only after assessing a response of oral prednisone and ruling out infectious causes • Intravitreal - triamcinolone and dexamethasone implant When should a patient start on chronic therapy? Guidelines for treatment Active uveitis – treat with high dose of corticosteroids¹ Add steroid-sparing agent if inflammation cannot be controlled with <10 mg prednisone within 3 months1

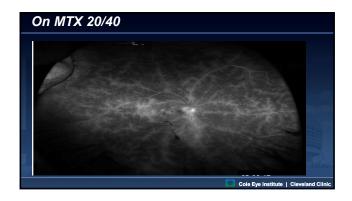
1. Jabs DA, et al. Am J Ophthalmol. 2000;130:492-513. (A)

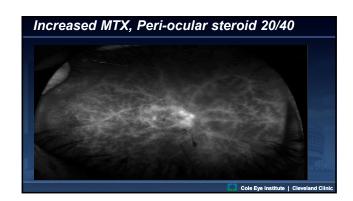
So who should get chronic therapy? Those who can't taper off prednisone Greater than 10 mg prednisone for greater than 3 months Those who have multiple flare ups (3 within 12 months) Those who you are controlling with just injections and vision is dropping 20/200 → IVK → 20/25 20/200 → IVK → 20/40 20/400 → IVK → 20/60

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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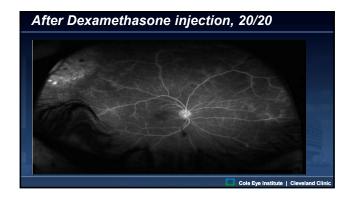
Gangaputra SS, Newcomb CW, Joffe MM, et al. Comparison Between Methotrexate and Mycophenolate Mofetil Monotherapy for the Control of Noninfectious Ocular Inflammatory Diseases. Am J Ophthalmol. 2019 The time to success was shorter (more favorable) for MMF than MTX (hazard ratio = 0.68, 95% confidence interval: 0.46-0.99). Proportion achieving success was higher for MMF than MTX from 2 to 8 months, then converges at 9 months. Onset of success was more than 3 months in both groups. Outcomes of treatment (MMF vs MTX) were similar across all anatomic sites of inflammation. The incidence of stopping therapy for toxicity was similar in both groups.

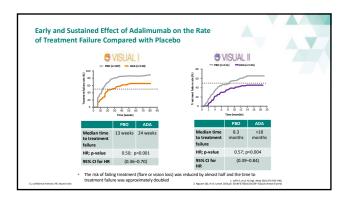
Is one superior to the other? Rathinam SR, Gonzales JA, Thundikandy R, et al. FAST Research Group. Effect of Corticosteroid-Sparing Treatment With Mycophenolate Mofetil vs Methotrexate on Inflammation in Patients With Uveitis: A Randomized Clinical Trial. JAMA. 2019 • 25 mg MTX vs 3 grams MMF. Treatment success was control at 6 months with less than 7.5 mg pred/2 drops a day of PF • Treatment success occurred in 66.7% patients in the methotrexate group vs 57.1% in the mycophenolate group (difference, 9.5% [95% CI, -5.3% to 21.8%]; odds ratio [OR], 1.50 [95% CI, 0.81 to 2.81]; P = .20). But almost 45% of patients had VKH Cole Eye Institute | Cleveland Clinic My first line therapy • Methotrexate or mycophenoloate mofetil (MMF) MTX – max dose of 25 mg, MMF max dose 3 grams daily • MTX – adults start 15-20 mg weekly, folic acid daily except on days of MTX. Check labs MMF – start at 500 mg bid, if tolerable (GI side effects), then push to 2 grams or 3 grams daily My ratio is about 50/50 Cole Eye Institute | Cleveland Clir How long do you give it work? Most data suggests 3-6 months for anti-metabolites to work • If disease can be controlled with a bridge of po steroids/intravitreal therapy then wait it out If flaring during use and it is vision threatening or requires high dose corticosteroids then I am switching therapy or supplementing



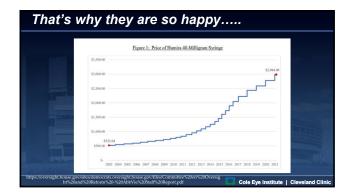


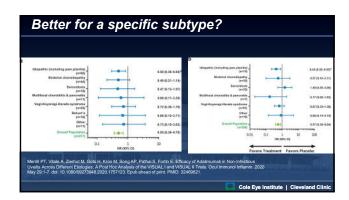




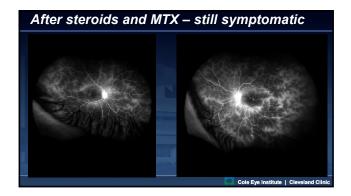


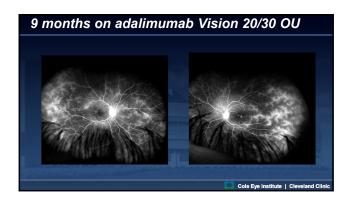


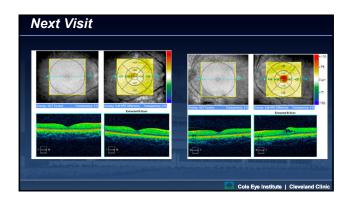


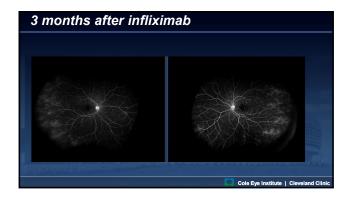


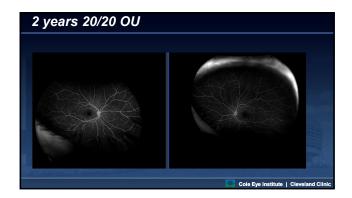
Suhler EB, Jaffe GJ, Fortin E, et al. Long-Term Safety and Efficacy of Adalimumab in Patients with Noninfectious Intermediate Uveitis, Posterior Uveitis, or Panuveitis. Ophthalmology. 2021 At study entry, 67% of patients (283/424) showed active uveitis and 33% (141/424) showed inactive uveitis;. At week 150, approximately 50% of patients (214/424) remained in the study. Patients showing quiescence increased from 34% (122/364) at week 0 to 85% (153/180) at week 150. Corticosteroid-free quiescence was achieved by 54% (66/123) and 89% (51/57) of patients with active or inactive uveitis at study entry. Mean daily dose of systemic corticosteroids was reduced from 9.4 ± 17.1 mg/day at week 0 (n = 359) to 1.5 ± 3.9 mg/day at week 150 (n = 181).





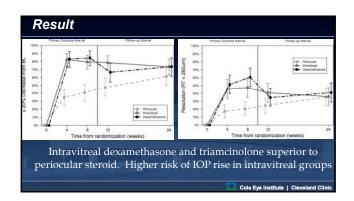




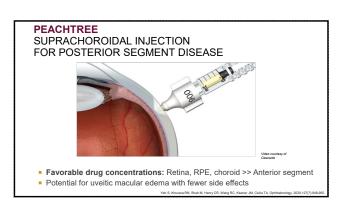


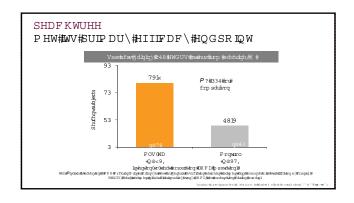
Burmester GR, Gordon KB, Rosenbaum JT, et al. Long-Term Safety of Adalimumab in 29,967 Adult Patients From Global Clinical Trials Across Multiple Indications: An Updated Analysis. Adv Ther. 2020 A total of 29,967 patients were included, representing 56,916 patient-years (PY) of exposure. Most frequent SAE of interest was infection (3.7/100 PY); The observed number of deaths was below what would be expected in an age- and sex-adjusted population for most adalimumabtreated patients. Lack of real-life data and limited long-term data (> 5 years) for most patients are limitations of this analysis.

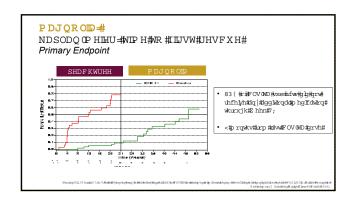
Local Therapy Options Topical Steroids (difluprednate vs prednisolone acetate) Periocular Steroids Intravitreal Steroids (triamcinolone, dexamethasone) Suprachoroidal Steroids (triamcinolone) Delivery implants Intravitreal injection (fluocinolone acetonide) Surgical implant (fluocinolone acetonide)

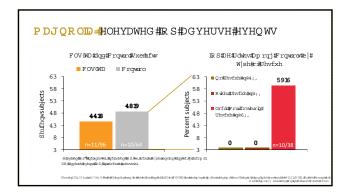






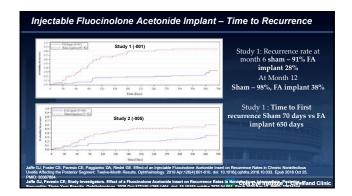






Fluocinolone Acetonide Implant Reduction in ocular inflammatory episodes 4% with recurrence at 1 year 10% at 2 yr and 20% at 3 yr 100% of phakic patients require cataract surgery 35% glaucoma surgery rate Callahan DC, et al. Arch Ophthalmol. 2008;126:1191-1201.

What about long-ter	m?
 Average time to recurren 	ce around 3 years
 Average time to reimplan original implant 	tation – 45-46 months from
 Re-implantation at original 	al site (or new site)
 Visual acuity post second improved 	l implantation generally stable or
Few complications	
Nicholson B et al AJO 2012	Cole Eye Institute Cleveland Clinic





1 year post intravitreal fluocinolone acetonide injection	
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So how do I use these therapies

- Difluprednate for short term treatment of aggressive anterior disease, CME, low-moderate grade intermediate uveitis
- Intravitreal steroids triamcinolone and dexamethasone for several month control in active posterior segment disease
 CME, retinal vascular leakage, active retinal lesions
- Those who need long term control fluocinolone acetonide implant (multiple recurrences, chronic CME, inability to taper steroid), injectable first line, then surgical for severe disease or vitrectomized.

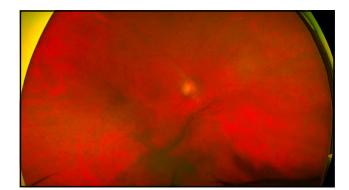
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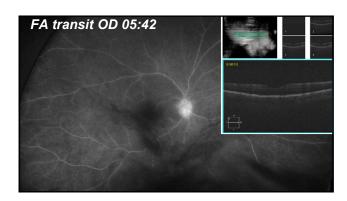
What signs should I worry about?

- When things don't respond they way I expect
 - High dose prednisone should quiet most inflammation
 - Infections that progress on therapy
- Necrosis of the retina, 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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Case Presentation 73 yo female decreased vision right eye for 2 weeks. Seen by outside retina specialist, had an AC tap for possible toxoplasmosis History of Breast CA, previous +ANA 1:320 2016, previous hip surgery years ago Renal failure due to lithium toxicity and s/p deceased donor kidney transplant 5 months ago –rATG, CMV D+/R+, EBV -/+ On tacrolimus, mycophenolate, prednisone 5 mg, pentamidine prophylaxis and difluprednate No previous history of COVID exposure... 20/200 OD, 20/20 OS, IOP 20, 14

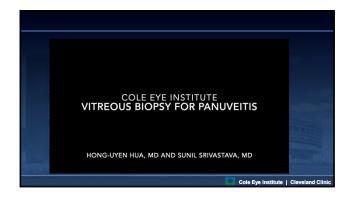




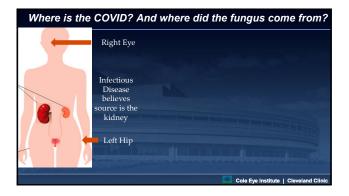
Thoughts? New onset slow unilateral vision loss with panuveitis on systemic immune suppression. No history of COVID exposure Toxoplasmosis Viral retinitis – CMV vs HSV Endophthalmitis – fungal/bacterial Inflammatory Medication Induced Maybe COVID.....?????? What next?

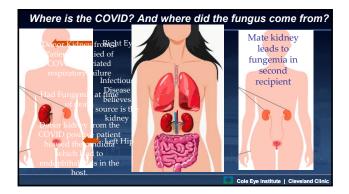
Next steps? Intravitreal tap & inject Send for: Toxo PCR, bacterial/fungal culture, CMV, HSV, VZV PCR if possible Inject: clindamycin, foscarnet, voriconazole





Biopsy Fungal Culture and PCR positive for Candida Albicans Infectious disease consult Started on oral fluconazole 800 mg → 400 mg daily Admitted for work up of candidemia Ortho team: left hip irrigation and debridement, head/liner exchange Synovial fluid cultures grew many candida albicans Blood culture +candida albicans, Urine culture – normal flora, Echo: normal EF, no valvular vegetations





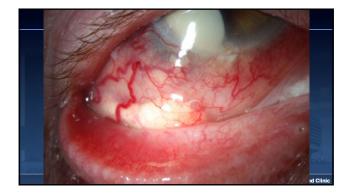


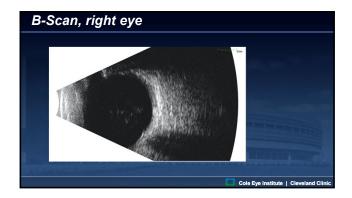


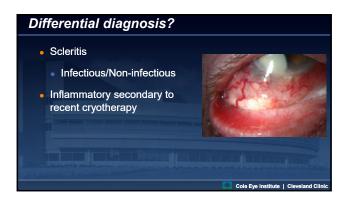
Endogenous Fungal Endophthalmitis • Consider in Elderly patient, Recently hospitalized patient IV drug users (even your neighbors can be IVDA) Patients with recent GI/GU infection Tap/inject or diagnostic PPV Treat with systemic anti-fungal (fluconazole 200-400 mg daily or voriconazole 200 mg bid) Cole Eye Institute | Cleveland Clinic Next case • Post op inflammation, gone wrong.... HPI • 71 yo female initially evaluated for conjunctival/corneal lesion prior to • Lesion was concerning for squamous cell carcinoma, now POM3 s/p excisional biopsy and cryotherapy Pathology: Epidermoid metaplasia (negative for carcinoma/dysplasia) Post-operative course complicated by chemosis and injection over the biopsy site, thought to be post-operative scleritis Managed initially with oral and topical steroids, then sub-Tenon's triamcinolone injection. Initially improved, then severely worsened – now referred

OD OS Dist VA sc HM at 3 feet → ph NI 20/60 → ph 20/50 IOP 9 10
Dist VA sc HM at 3 feet → ph NI 20/60 → ph 20/50
IOP 9 10
Pupils Irregular, minimally Round and reactive reactive
Visual Field Full Full
EOM Full Full





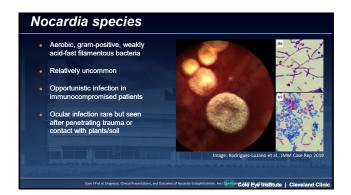


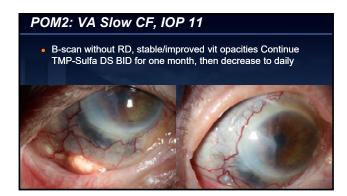


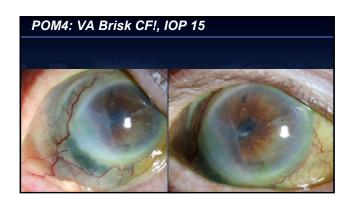
Management
Taper off of oral steroid
 Anterior chamber tap and intravitreal injection of antibiotics/ antifungals
 Anterior chamber washout/biopsy with possible scleral patch graft given degree of scleral thinning
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Started on sulfamethoxazole-trimethoprim 800-160 mg (TMP-Sulfa) BID at time of surgery; amikacin injected at time of surgery along with vancomycin and voriconazole Culture positive for Nocardia cyriacigeorgica Negative fungal cultures Continue TMP-Sulfa DS BID Start amikacin 2.5% q2h while awake Start linezolid 0.2% q2h while awake









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 and develops sudden floaters and vision loss Diagnosed with candida endophthalmitis but progressive worsening of vision Transferred – ophtho resident called

• Vision 20/200 OD 20/20 OS
Tr AC cell
DFE: see photos
But first – I will show you his mouth
Cole Ein Institute, I. Claveland Cillate



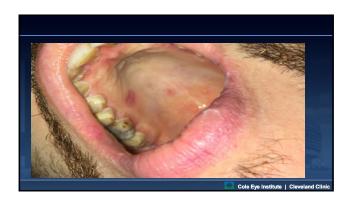




So my resident thinks	
This does not make sense	
What would Sunil do?	
Recheck everything	
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Multiple ischemic areas Looks like artery occlusions Can systemic fungal infection give you artery occlusion? Maybe but rare, and no lesions OS, and no full thickness lesions But inflammatory disease can. Let me look at his mouth again





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



uccess!	
Oral ulcers, genital ulcers, retinitis = Behcet's	
	_
Cole Eye Institute Cleveland Clinic	
ase 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.	
Cole Eye Institute Cleveland Clinic	
ummary	
 Properly identification location of inflammation, talk to patients and then order appropriate labs 	
 No cookbook, but a couple of basics we should order (Tb, 	
Syphilis, Sarcoidosis)	
Consider medications (systemic and local) as causes	

Lots of options for long term control in uveitis patients
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