Rapid Fire Referral Grand Rounds

COPE#81858-TD

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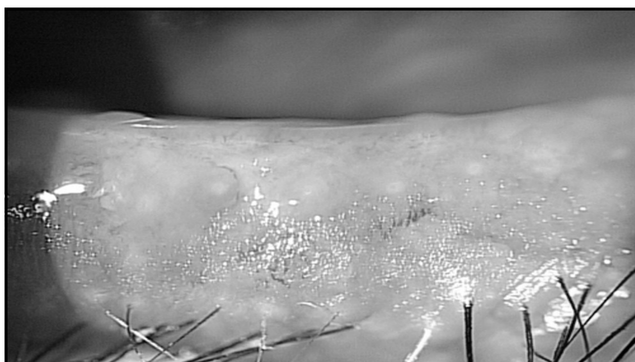

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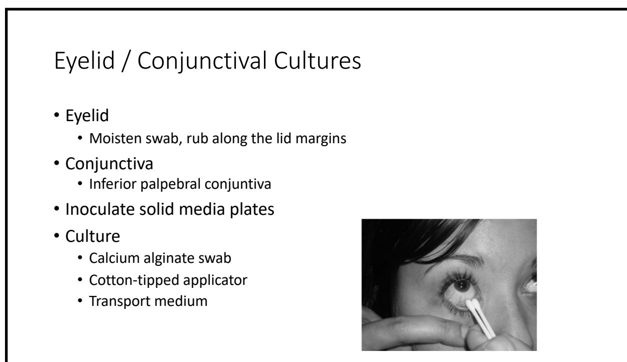

Eyelid / Conjunctival Cultures

- Eyelid
  - Moisten swab, rub along the lid margins
- Conjunctiva
  - Inferior palpebral conjuntiva
- Inoculate solid media plates
- Culture
  - Calcium alginate swab
  - Cotton-tipped applicator
  - Transport medium

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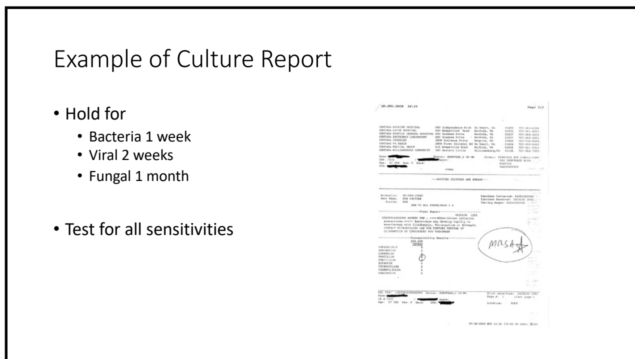

Example of Culture Report

- Hold for
  - Bacteria 1 week
  - Viral 2 weeks
  - Fungal 1 month
- Test for all sensitivities

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Treatments for MRSA

- 100% to vancomycin[1]
- 97.7% to sulfisoxazole[1]
- 95% to Polytrim[2]
- 93.2% were sensitive to tetracycline[1]
- 63.6% were sensitive to bacitracin[1]
- 14.8% of MRSA isolates were sensitive to ciprofloxacin and erythromycin[1]
- Besivance has been reported to be effective

1. Freidlin J, Acharya N, Lietman TM, et al. Spectrum of eye disease caused by methicillin-resistant staphylococcus aureus. Am J Ophthalmol. 2007 Aug;144(2):313-5
2. Asbell PA Colby KA Deng S, et al. Ocular TRUST: nationwide antimicrobial susceptibility patterns in ocular isolates. Am J Ophthalmol. 2008 Jun;145(6):951-58.

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Indications for Cultures

- Hyperacute conjunctivitis
- Neonatal conjunctivitis
- Post-operative infections
- Chronic conjunctivitis
- Central corneal ulcers
- Membranous / Pseudoconjunctivitis
- Preseptal / Orbital cellulitis
- Post-traumatic infections
- Marginal infiltration / ulceration
- Atypical external disease
- Severe dry eye
- Bullous keratopathy
- Axial and severe keratitis

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Case Example

- The 84 year old, AA female presents for 3-4 month DES check (no touch) and MMP-9 testing. Pt has a h/o DES and POAG mild OU. Pt states OS>OD has some itching. Pt states she has only been using her cyclosporine 0.05% and AT's. She never picked up fluorometholone drops and is not using AT's ointment or a heat mask.

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- Ocular Hx:
  - Dry eye syndrome – 10+ yrs
  - Herpes stromal keratitis OS
    - Inactive – Last episode 2020
  - Anterior scleritis OS
    - Inactive
  - POAG - Mild OU
  - Pterygium sx OU
  - Phaco / istent OU
  - Previous treatments
    - Amniotic membrane OS (2019, 2020)
    - Punctal cautery (2011) OU
    - PGA OU
- Med Hx:
  - NIDDM 15 yrs
  - Osteoarthritis
  - Hypothyroid
  - Seasonal allergies
- Meds:
  - Ceterizine
  - Lactulose
  - Levothyroxone

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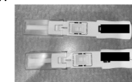
Clinical Exam

- Lids / Lashes – Clear and good position
- Conjunctiva – tr injection OU
- Cornea
  - OD 2+ Inf SPK
  - OS Dense SPK, 1+ K edema
- A/C – Deep and Quiet
- PCIOL OU
- IOP – 11 mmHg OU
- K Sensitivity – OD Normal OS Reduced



Anything else we should add???

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Do you test for K sensitivity?

If so, how?

Central vs. S/I/N/T/C??

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Corneal Sensation

- Greatest in the central cornea (elderly patients - more sensitive in the periphery)
- Drops rapidly as distance increases from the limbus
- Falls with increasing age
- Is not affected by iris color
- More sensitive in the temporal limbus than the inferior limbus
- Reduction has been reported in diabetes type 1 and type 2

Faulkner WJ, Varley GA. Corneal diagnostic techniques. In: Krachmer JH, Mannis MJ, Holland EJ, eds. Cornea. 2nd ed. Vol. 1 Philadelphia: Elsevier/Mosby; 2005:229-235.
External Disease and Cornea, Section 8. Basic and Clinical Science Course, AAO, 2010.

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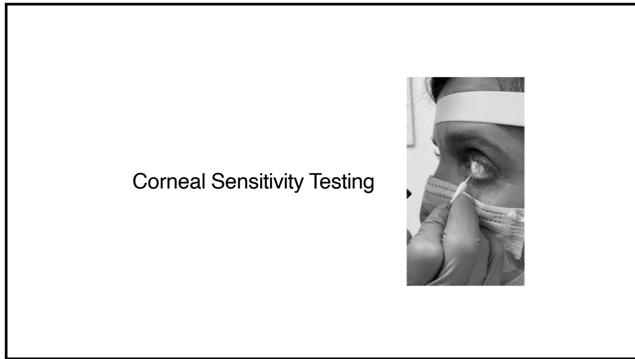

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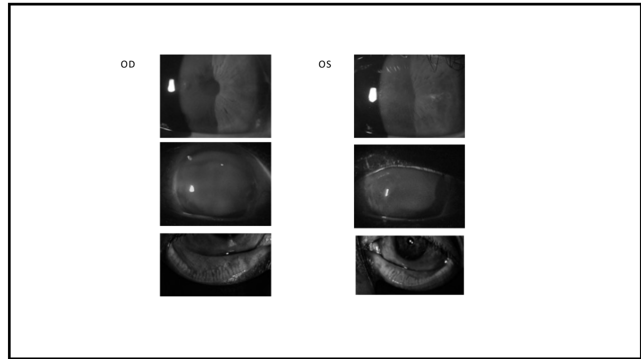

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Neurotrophic Keratitis: Classification

Mackie classification

- Stage I is characterized by hyperplasia and/or irregularity of the epithelium, evolving to punctate keratopathy, corneal edema, neovascularization, stromal scarring.
- Stage II is defined by a recurrent or persistent epithelial defects or a PED without stromal thinning.
- Stage III: stromal involvement leads to corneal ulcer, melting and perforation

Mackie IA. Neuroparalytic keratitis. Current Ocular Therapy. Philadelphia, PA: WB Saunders; 1995:452-4.

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Stage 1
Rose bengal staining of the inferior palpebral conjunctiva
Decreased TBUT
Increased mucous viscosity
Punctate corneal epithelial fluorescein staining (resembles dry eye)

Mackie IA. In: Fraunfelder F, Roy FH, Meyer SM, eds. Current Ocular Therapy. WB Saunders, 1995.

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Stage 2
Epithelial defect • Typically oval in shape • In central/inferior cornea • Surrounded by a rim of loose epithelium • Edges may become smooth and rolled
Stromal swelling with folds in the Descemet membrane
Anterior chamber inflammatory reaction may be present

Mackie IA. In: Fraunfelder F, Roy FH, Meyer SM, eds. Current Ocular Therapy. WB Saunders, 1995.

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Stage 3
• Corneal ulcer
• Stromal lysis/melting
• Perforation

Mackie IA. In: Fraunfelder F, Roy FH, Meyer SM, eds. Current Ocular Therapy. WB Saunders, 1995.

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Endogenous nerve growth factor (NGF) and its role in NK:

impaired trigeminal corneal innervation

- ↓ Lacrimation and blink reflex
- ↓ Epithelial cell vitality, metabolism, mitosis
- ↓ Epithelial trophism and repair
- ↑ Stromal and intracellular edema
- ↓ Microvilli
- ↓ Development of the basal lamina

Mastropasqua et al. (2017) J Cell Physiol 232:717-24

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Endogenous NGF Maintains Corneal Integrity By Three Mechanisms

Endogenous nerve growth factor acts through specific high-affinity (ie, TrkA) and low-affinity (ie, p75NTR) nerve growth factor receptors in the anterior segment of the eye to support corneal innervation and integrity.[1]

SHOWN IN PRECLINICAL MODELS[1]

CORNEAL INNERVATION

NGF plays a role in nerve function and stimulates the regeneration and survival of the sensory nerves[2,3]

TEAR SECRETION

NGF binds receptors on lacrimal glands and promotes sensory-mediated reflex tearing secretion[1,4]

CELL PROLIFERATION AND DIFFERENTIATION

NGF stimulates proliferation, differentiation, and survival of corneal epithelial cells[1]

1. Mastropasqua L, Massaro-Giordano G, Nubile M, Sacchetti M. Understanding the pathogenesis of neurotrophic keratitis: the role of corneal nerves. *J Cell Physiol.* 2017 Apr;232(4):717-724. 2. Müller LJ, Marfurt CF, Kruse F, Tervo TM. Corneal nerves: structure, contents and function. *Exp Eye Res.* 2003 May;76(5):521-42. 3. Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol.* 2014;8:571-9. 4. Muzi S, Colafrancesco V, Sornelli F, et al. Nerve Growth Factor in the Developing and Adult Lacrimal Glands of Rat With and Without Inherited Retinitis Pigmentosa. *Cornea.* 2010;29:1163–1168.

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Severity-Based Therapy

Stage	Therapy
1	• Preservative-free artificial tears formulations • Punctal occlusion • Hydrogel contact lens (consider large diameter) • Recombinant human NGF (rhNGF, cenegermin) • Serum/plasma/platelet rich plasma
2	Supportive therapies plus: • rhNGF • Scleral lens (± serum/plasma) • Amniotic membrane • Botulinum induced ptosis, Tarsorrhaphy
3	• rhNGF • Keratoplasty + scleral lens, tarsorrhaphy, neurotization

Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol*. 2014;8:571-579. Sheha H, Tighe S, Hashem O, Hayashida Y. Update on cenegermin eye drops in the treatment of neurotrophic keratitis. *Clin Ophthalmol* .2019;13:1973-1980. Published Oct 7, 2019.

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Serum /Plasma Therapy

- **Serum/plasma have reported efficacy as primary or adjunct therapy**
  - Reported success of serum alone (20-50% concentration) ranges from 71 to 100% within 90 days (Guadilla et al. Arch Soc Esp Offalmol 2013; Jeng and Dupps Cornea 2009; Pflugfelder *AJO* 2006)
  - Umbilical cord serum may be more effective and has higher concentrations of substance P and NGF than peripheral blood serum (Yoon KC et al. *Ophthalmology* 2007)
  - Epithelial defect healed in 97.4% of stage 2-3 NK after 11 weeks of plasma rich in growth factors (PRGF) (Sanchez-Avila RM et al. *Int Ophthalmol* 2018)
  - Serum can be used safely in combination with SiH CL. No inflammation or CL deposits were observed (Choi JA *ECL* 2011)

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Amniotic Membrane

- Randomized clinical trial reported healing of refractory neurotrophic ulcers with conventional therapy (lubrication plus BCL or tarsorrhaphy) or amniotic membrane transplant (AMT). Healing rates were similar in the 2 groups: 67% with conventional therapy and 73% with AMT (Khokhar S et al. Cornea 2005)
- AMT was also equivalent to autologous serum (AS) in healing neurotropic ulcers: 70% for AS and 73% for AMT (Turkoglu E et al. Semin Ophthalmol 2014)
- Multilayer AMT recommended for deep ulcers and Descemetoceles (Kruse F et al. Ophthalmology 1999)

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Scleral Lenses

- Use of fluid filled scleral contact lenses for treatment of NK initially reported decades ago (Romero-Rangel et al. *AJO* 2000)
- Non-healing corneal epithelial defects with BCL healed without recurrence in all 9 eyes treated with PROSE scleral lens (Ling J et al. *Am J Ophthalmol* 2013)
- Overnight wear (with close monitoring) may accelerate healing (Lim P et al. *AJO* 2013)

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Corneal Neurotization

- Corneal sensitivity restored after sural nerve grafts (Elbaz et al. *JAMA Ophthalmol* 2014)
- Free sural nerve graft was coapted end-to-side with supratrochlear nerve and the distal portion of the nerve was separated into fascicles that were distributed around the limbus
- Corneal sensitivity, measured pre- and post-op with the Cochet-Bonnet esthesiometer, returned to normal after 5

PRE POD 91 POD 161

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Treatment

- Continue:
  - Cyclosporine 0.05% BID OU
  - Heat Mask
- Stop
  - Oral ceterizine
- Order
  - Cenegermin 20 mcg/mL – Patient to call once meds come in to review meds / demo proper usage
  - Ceterizine ophth sol BID OU
- Follow Up
  - 3-4 months glaucoma / Dilate OCT - G

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cenegermin-bkbj 20 mcg/ml was approved by FDA in August 2018

Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis

- Approved for the treatment of neurotrophic keratitis in adults and children age 2 and older
- Available for ordering since January 2019
- Developed by Dompé pharmaceuticals, available through specialty pharmacy

Bonini S, Lambiase A, Rama P *et al.* Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis. *Ophthalmology* 2018;125:1332-1343.

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Study Conclusions

Up to 72% of patients achieved complete corneal healing;

80% of healed patients were recurrence free after 1 year*

After 8 weeks of treatment, 6 times daily

In the majority of patients across two clinical studies (cenegermin ophthalmic solution 0.002%) was well tolerated and more effective than vehicle in promoting complete corneal healing of moderate or severe NK.

50 clinical trial sites in Europe and the U.S.

Study NGF0212 (REPARO) (N=52 per group) European patients with NK in one eye NCT01756456 — **72.0%** completely healed; Vehicle response rate 33.3%

Study NGF0214 (N=24 per group) U.S patients with NK in one or both eyes NCT02227147 — **65.2%** completely healed; Vehicle response rate 16.7%

Of patients who healed after one 8-week course of treatment… **80%** Remained healed for one year*

*Based on REPARO, the study with longer follow-up

1. Bonini S, Lambiase A, Rama P *et al. Ophthalmology* 2018;125:1332-1343.
2. Chao W, J. BDC, R. D *et al.* Data on file. Healing of persistent epithelial defects or corneal ulcers by recombinant human nerve growth factor eye drops in patients with stage 2 or 3 neurotrophic keratitis. Presented at: Congress of the European Society of Ophthalmology (SOE) 10–13 June, 2017, Barcelona, Spain. 2017.

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Emergency Immediately	Very Urgent Few Hours	Urgent Within a day
Retinal Artery Occlusions	***Perforation***	Orbital Cellulitis
Chemical Burns	***Ruptured***	***Orbital Injury***
	Acute Glaucoma	Corneal Ulcer
	Sudden Proptosis	***Corneal Abrasion***
		Hyphema
		Intraocular Foreign Body
		Retinal Detachment
		Macula Edema

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Which Imaging Test is Appropriate for Recent Onset Orbital Trauma?

A. Ultrasonography
B. Computed tomography
C. Magnetic resonance imaging
D. Positron emission tomography

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General Trauma Considerations

- Take care of the obvious
  - ABCDE's
  - Radiology
  - Concussion evaluation
  - Mental status of patient

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Importance of History

- Stop….. ***Emergency***… if chemical burns, proceed to provide copious irrigation before history and physical or exam is done
- Take your time with the history
- Nature of insulting object
  - Sharp, dull, big, small
- What was your vision before the injury?

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Evaluation of Ocular Trauma

- Visual acuity
- Pupil testing
- Confrontation visual fields
- EOMs
- Gross examination
- Slit lamp examination
- Tonometry*
- Dilation*
- B-scan ultrasonography*
- Color vision
- Imaging studies

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Computerized Tomography

- If you suspect any of the following, a CT scan is indicated
  - History of loss of consciousness for more than 10 minutes
  - Alcohol intoxication
  - History of seizures
  - Unreliable history of the accident
  - Age less than 2 years
  - History of persistent vomiting
  - Bleeding from the nose, mouth or ear
  - Patient has serious facial injury
  - Penetrating injury to the skull
- No MRI for fear of metallic foreign body

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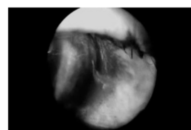
Open Globe

- Check VA - reduced
- Seidel's sign
- Displaced / peaked pupil
- Non-reactive pupil
- Low IOP
- Poor reflex
- Hyphema



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Weekend Call

- 64 yowm c/o decreased VA OS, watery eye, no pain
- Hit head on corner of the bed last night
- Went to sleep hoping it gets better
- Used ATs for relief
- Ocular Hx: Cataract surgery OU, PKP OS 2005

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Chemical Burns

- ***Emergency!!!*** - Every minute counts
- Do not waste time on Hx and PE
- Alkali burns more common and worse than acid
  - Alkali
    - Household cleaners, fertilizers, drain cleaners
  - Acid
    - Industrial cleaners, batteries, vegetable preservatives

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Chemical Burns

- Absolute Emergency
- Immediate irrigation
- Check VA
- Check pH if possible

Photo accessed from http://www.globalspec.com/ImageRepository/LearnMore/20124/PH-Scale3125510458de479190dd027baaf7a2c2.png

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Management of Chemical Burns

- Debride necrotic tissue
- **Frequent ATS**
- Bandage contact lens
- **Quinolone: 1 gtt 4-6x/day (prevents infection)**
- Prednisolone phosphate: 1 gtt q 1-2 hr while awake (reduces inflammation)
- Vitamin C: 1-2 gm po QD (reduces corneal thinning/ulceration)
- 10% sodium citrate: 1 gtt q 2 hr while awake (chelates Ca++ and impairs PMN chemotaxis)
- **Scopolamine 0.25%: 1 gtt TID (reduces pain/scarring with AC inflammation)**
- 10% Mucomyst (n-acetyl-cysteine): 1 gtt 6x/day (mucolytic agent and collagenase inhibitor)
- **Oral pain meds**
- Doxycycline 100 mg po bid (collagenase inhibitor)
- **Glaucoma gtts/oral diamox if IOP elevated**
- Significant injury may require admission

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Pearls - Prevention is KEY!!!

- Know the potential eye safety dangers
- All chemical injuries should be lavaged immediately
- Extent of damage is dependent on concentration and pH of acid or base
- Eliminate hazards before starting work
- Use protective measures

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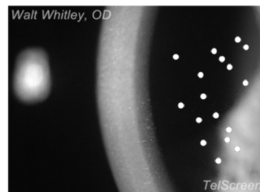
"The Common Eyeritis"

- 32YOWM, Red, Painful Eye OD, Photophobic, No discharge
- No previous episodes
- Ocular/Medical Hx: Unremarkable
- No other associated symptoms
- SLE: 2+ injection / 2+ cells



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Case Example

- 44yo Asian American c/o blurred VA, redness, tearing, peri-orbital edema starting 2-3 days prior
- Med Hx: Uncontrolled DM (Dx in 1998)
- Vasc: OD 20/60 PH 20/30
  OS 20/80 PH 20/40
- IOP: 21 / 18

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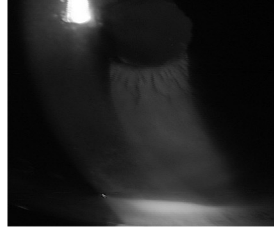
Hypopyon

- HLA B27
- Bechet's
- Infectious uveitis
- CL Related



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What is Your Treatment?

- Prednisolone acetate 1% vs. difluprednate 0.05% vs. loteprednol etabonate .5%
- Homatropine 5% vs. Scopolamine 0.25% vs. Atropine 1%
- Would you consider lab testing?
- Would you prescribe an oral medication?

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Case Example

- Acute, non-granulomatous, anterior uveitis OS
- Cause???
- Treatment
  - Ordered labs – CBC w/diff, ESR, SMA-12, HLA-B27, Urinalysis, FTA-ABS, RPR, Lyme Western Blot
  - Difluprednate q2h OS
  - Homatropine 5% TID OS
  - Doxycyline 100 mg BID po

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Pulse Therapy

- QID to Q 1 Hour for 7 to 10 Days
- Zero Tolerance for AC Cells
- Avoids Surface Toxicity
- Quick & Dirty
- Hit It Hard and Fast: Aggressive

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Doxycycline

- Inhibits bacterial protein synthesis
- Cannot be used for kids <8 and pregnancy/nursing
  - Category D
- Anti-infective dose: 100 mg BID for 10 days
- Anti-inflammatory dose: 50 mg BID for one month then qd 1-3 months
- Side effects/Contraindications:
  - GI upset: caution patient to take this with food
  - Photosensitivity
  - Pseudotumor cerebri

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Lyme Titer

- Erythema migrans is the only manifestation of Lyme disease in the United States for which clinical diagnosis should be made in the absence of laboratory confirmation
- A patient with a significantly characteristic symptom with the appropriate history of possible exposure should be started on antibiotics after appropriate laboratory studies have been drawn

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Tx for Lyme Disease

- Early infection or nonspecific symptoms with positive Lyme titers in the adult may be treated with:
  - Doxycycline 100 mg BID x 14 days
  - Amoxicillin 500 mg TID x 14 days
- Severe infection in adults with definitive ocular, neuro-ophthalmic, neurological, or cardiac involvement may be treated with penicillin G (24 million units, intravenous, daily in four divided doses for 21 days) or intravenous ceftriaxone (2 g/day in two divided doses for 21 days)

Wormser et. Al. The Clinical Assessment, Treatment, and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesios is: Clinical Practice Guidelines by the Infectious Diseases Society of America. *Clinical infectious diseases. Vol. 43. Issue 9.*

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When Should Lab Tests Be Ordered?

- Bilateral cases
- Atypical age group
- Recurrent uveitis
- Recalcitrant cases
- Hyperacute cases
- Worsens with tapering
- VA worsens
- Immunosuppressed

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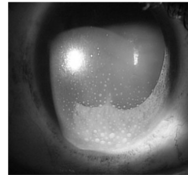
Uveitis: Common Systemic Associations

- Most common cause
  - Idiopathic : 38-70%
- Other systemic causes
  - HLA-B27 related disease
  - Sarcoidosis
  - Systemic Lupus Erythematosus
  - Rheumatoid Arthritis
  - Behcets Disease



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Lab Testing

- Minimum lab testing
  - CBC with differential
  - Erythrocyte sedimentation rate (ESR)
  - Angiotensin converting enzyme (ACE)
  - Venereal disease research laboratory (VDRL)
  - Fluorescent treponemal antibody absorption (FTA-ABS)
  - Lyme titers in endemic areas
  - HLA-B27
  - Antinuclear antibody (ANA)
  - Rheumatoid factor
  - Urinalysis
  - Chest X-ray
  - PPD or Quantiferon TB Gold
  - MRI

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Condition	Clinical Features	Test Indicated
Ankylosing spondylitis	Young male, low back pain, chest pain	HLA-B27, sacroiliac X-ray
Reactive syndrome	Young male, arthritis, urethritis, conjunctivitis	HLA-B27, ESR, CRP
Juvenile idiopathic arthritis	Slight female predilection, joint pain >6 weeks	ANA, RF, knee radiograph
Inflammatory bowel disease	Ulcerative colitis, diarrhea, abdominal cramps	HLA-B27, GI referral for endoscopy
Sarcoidosis	African Americans, females, vasculitis, vitritis	ACE, chest X-ray or CT scan
Tuberculosis	Prolonged cough, fever, chills, night sweats, weight loss	PPD, chest X-ray
Syphilis	Hx of sexual contact with infected person, rash, fever, malaise, headache, joint pain	FTA-ABS, VDRL, RPR
Toxoplasmosis	Immunocompromised status, exposure to cats, hx of eating raw meat, punched-out retinal lesions	Toxoplasma IgG or IgM for acute acquired cases
Lyme disease	Recent tick bite	Lyme Western Blot

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82 yowf Sudden Loss of VA OD

- Ocular history:
  - Primary open angle glaucoma OU
  - Epithelial basement membrane dystrophy OU
  - Pseudophakia OU
  - Early Dry ARMD OU
- Medical history:
  - Arthritis
  - Hypertension
  - High Cholesterol
  - Peripheral Neuropathy
  - Restless leg Syndrome
  - GERD

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- Ocular Medication
  - Brim/Tim BID OS
  - Travaprost QHS OU
- Systemic Medication
  - Crestor 5mg
  - Amlodipine-Benazepril 5/10mg
  - Pramipexole 0.125mg
  - Tramadol HCL
  - Nexium 40mg
  - Lidoderm patch
  - Gabapentin 300mg
  - Celebrex 200mg
  - Iron supplement
  - Krill oil supplement

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Case Example

- VAcc:
  - OD: LP
  - OS: 20/50 +2
- Pupils
  - OD: 1+ APD
  - OS: round and reactive
- EOM
  - Full OU
- CVF
  - OD: constricted inferior 180
  - OS: Full to finger counting
- IOP: 18mmHg/18mmHg by Goldmann

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PW-GCA

- Assessment
  - Ischemic Optic Neuropathy OD
    - Pt denied any jaw pain, headaches, shoulder or hip pain, change in weight and malaise
- Plan
  - Labs ordered: ESR, CRP, CBC w/diff
  - Medication: Prednisone 20mg 3 PO
  - Meds are not to be started before having blood drawn
  - Follow up in 1 week pending lab results

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PW - GCA

- Lab Results:
  - ESR: 95 (High)
  - CRP: 7.09 (High)
  - Platelet: 465 (High)
- Temporal artery biopsy scheduled in 2 weeks

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PW -GCA

- Temporal Artery Biopsy Result
  - Active arteritis with rare giant cells, consistent with temporal arteritis
  - Mild arteriosclerosis
  - Disruption and focal loss of internal elastic lamina
- Informed the patient that her PCP will monitor her labs from now on and adjust her oral prednisone dose accordingly. She is to continue on the 60mg/day dosing for right now until he instructs her otherwise
- Follow up in 1 month

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Prednisone

- Suppresses inflammatory cascade and immune response
- Optic neuritis
  - Methylprednisolone 1g/day i.v. for 3 days
  - 60-100mg qd p.o. for 11 days
  - Only after initial IV steroid treatment per ONTT to decrease risk of recurrence
- AION: 60-100mg qd
- Scleritis/Uveitis
  - Not responding to topical treatment
  - 40-80 mg as an initial dose with taper

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Prednisone

- Side Effects/Contraindications:
  - Increased IOP
  - Cataract formation
  - Fluid retention (moon face, buffalo hump)
  - Increase blood sugar levels in diabetics
  - Gastric ulcers
  - Not to be used if pregnant
  - Mood changes
- Advantages:
  - Widely available
  - Inexpensive

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Oral Corticosteroid Considerations

- Accurate diagnosis is essential
- Indicated for acute inflammatory eye, orbital and eyelid conditions
- Pregnancy category C
- Dosepaks available
  - 24 mg, 30 mg, 60 mg with taper
- Best taken with meals
- Short term rarely has ocular side effects

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Clinical Pearls

- All visual fluctuations are related to ocular surface disease
- Consider time course of events
- Consider cultures if NI
- Communication is key to successful collaboration!!

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Thank You!!!

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