

## ***Melton – Thomas Clinical Grand Rounds (2)***

Ron Melton, OD, FAAO  
Randall Thomas, OD, MPH, FAAO  
www.eyupdate.com

### **Financial Disclosure**

Dr. Ron Melton and Dr. Randall Thomas are consultants to, on the speakers bureau of, on the advisory committee of, or involved in research for the following companies: ICARE, B+L

### **Shingrix May Replace Zostavax®**

- Shingrix is the 2nd vaccine to be FDA approved to help prevent shingles.
- Approved for people aged 50 and older
- A non-live vaccine (Zostavax is live, attenuated)
- Administered in 2 - I.M. doses (initially then 2-6 months later)
- About 90% effective and maintained over four years
- If the last Zostavax vaccine was at least 5 years ago, can have Shingrix
- Marketed by GlaxoSmithKline

### **Latest on Shingles**

- Mean age of event: 52
- Patients who have had HZO should be examined “within several weeks before and after vaccination against herpes zoster” because they may be at risk for recurrent eye disease.
- We should “recommend strongly” that patients over 50 get Shingrix.
- Our advocacy could “play an important role in increasing vaccination rates.”
- About 10% of people have a reaction to Shingrix, more after the second dose.

Reference: Ophthalmology, Nov 2018

### **Update on Shingles**

- Incidence is on the rise, and at increasingly earlier ages
- Postherpetic neuralgia occurs in about 30% of patients with HZO, mostly in older people
- Shingrix is about 90% effective
- “Although eye doctors often view recommending vaccinations as the job of the PCP, given the incredible toll that HZ can take on the eye, we must take responsibility for protecting our patients and recommending this preventive measure.”

Reference: Ophthalmology, Nov 2018

### **Solar and Laser Retinopathy**

- Similar pathophysiology: DDx- good Hx
- Central scotoma with mild to moderate reduction in BVA
- Small, focal yellowish macular lesion
- OCT: Compromise to RPE and outer layers
  - » Inner layer involvement in severe damage
- Light energy is absorbed by RPE resulting in heat damage to the tissue
- Some recovery of vision may occur over several months

## Hand-Held Laser Retinal Injury

- Delay in diagnosis is a common feature.
- Average age of exposure 9-16 years, mostly males. 50% admit to laser exposure.
- Vision decrease highly variable; modest recovery over time.
- Symptoms: Central scotoma, variable blurred vision.
- OCT is critical to the diagnosis; Focal RPE and outer retinal tissues are preferentially damaged.
- "The lack of awareness of such injuries among ophthalmologists is likely to contribute toward a delay in making the diagnosis, as evidenced by the fact that almost a third of children in this study were referred as retinal dystrophies." This is likely true for most eye doctors.

Raoof N, et al. *Am J Ophthalmol*. 2016;171:88-94

## Bacterial Conjunctivitis

- Unilateral or bilateral red eye(s) with purulent or mucopurulent discharge of varying degree
- In subtle cases, carefully examine the lacrimal lake under high magnification and look for microparticulate debris which can be evidence of bacterial infection.
- Preauricular lymphadenopathy is uncommon, but can be present in hyperacute cases
- Chemosis may be present in more severe cases
- SPK can be present, especially if staphylococcal etiology. This is usually the result of staph exotoxin chemotoxicity, and tends to be seen mostly inferonasally because of tear film dynamics
- Common etiology: *Adults*: Staph aureus, Staph epidermidis, Strep pneumoniae  
*Children*: Strep pneumoniae, Haemophilus
- Therapy: *Adults*: Tobramycin, Polytrim, or Fluoroquinolone  
*Children*: Polytrim or Azasite solution or Polysporin ung
- Treat for five to seven days as a rule

## Superior Limbic Keratoconjunctivitis

- Both sexes affected, women more
- Main symptoms: distressingly irritated eyes
- Dry eyes common companion finding
- Symptoms disproportionate to clinical findings
- Spontaneous exacerbations and remissions
- 25-40% have some thyroid dysfunction
- Tx: difficult- .5% AgNO<sub>3</sub>, optimum lubrication, pressure patching, therapeutic soft lenses, surgical resection, cryotherapy

## The Eye and the ED

- Why people go to the ED with Eye problems

Most common ICD Diagnosis

<i>Conjunctivitis</i>	33%
<i>Corneal injury</i>	13%
<i>Corneal F.B.</i>	8%
<i>Hordeolum</i>	4%

- Mean ED charge \$989.30 for eye visit
- Eye visits: 1.5% of all visits
- 32,000 eye-related visits per year

Vazini K, et al. *Ophthalmology* 2016;123(4):917-19

## Adenoviral Infections

- Common cause of "red eyes"
- Assume adenovirus until proven otherwise
- Often have pre-auricular node
- Non-purulent watery discharge
- Usually starts in one eye and spreads to fellow eye in a few days
- Always evert lids to survey tarsal conjunctiva
- With EKC, spotty sub-epithelial infiltration in 50 to 75% of untreated cases

## Literature on Adenoviral Keratoconjunctivitis

- Pseudo-membranes are a frequent complication of EKC
- In untreated cases, 50% of corneas develop subepithelial infiltrates – a cellular immune reaction against viral antigens
- AdenoPlus® is highly sensitive, specific, simple and inexpensive
- Bacterial superinfection is rare
- "Topical steroids relieve symptoms, and 5% betadine kills the virus in tears, thus reducing the risk of disease spread."
- Restasis does not affect the natural course of the disease.

Jhanji V, et al. *Survey Ophthalmol*. 2015;60(5):435-43

## Perspective on Betadine

- “The instillation of 5% povidone iodine solution in the conjunctival sac to prevent endophthalmitis has been shown to be effective and has been widely used for decades.”
- “One in three ASC’s prepares the 5% solution by diluting commercially available 10% povidone-iodine with saline solution. This practice has been shown to be safe and effective despite the labeling ‘do not use in the eye’ present on the 10% Betadine solution.”

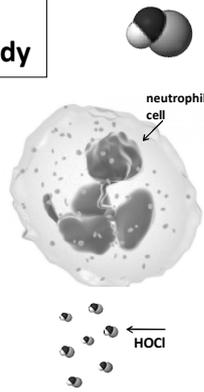
OSN 9-10-15

## Hypochlorous Acid

- Pure hypochlorous acid (HOCl) is released from neutrophils
    - » Essential part of body’s immune response
  - In the body, HOCl:
    - » Kills microorganisms
    - » Neutralizes inflammatory toxins released from pathogens
    - » Helps suppress the body’s inflammatory response
    - » Prevents biofilm formation
  - Ophthalmic strength HOCl has comparable microbial spectrum to Betadine
  - Covers some bacterial strains missed by Betadine (*Serratia marcescens*)
  - Onset of activity twice as fast as Betadine (1 min vs 2 min)
  - Remains active with a toxicity level 1000x lower than Betadine
- Antimicrobial Activity Comparison of Pure Hypochlorous Acid (0.01) with other Wound and Skin Cleansers at Non-Toxic Concentrations. Hoon, Rani, Najafi, Wang, Debabov; SAWC Spring 2013 and WHD*
- Klocek, M.S., et al. Time-Kill Comparison of Povidone Iodine to Hypochlorous Acid Against Endophthalmitis Isolates of Staphylococci. ARVO Annual Mtg 2016 Abstract Number 5861*

## The Role of Pure Hypochlorous Acid in the Body

- Pure hypochlorous acid (HOCl) is released from neutrophils
  - » Essential part of the body’s immune response
- In the body, HOCl:
  - » Kills microorganisms
  - » Neutralizes inflammatory toxins released from pathogens
  - » Helps suppress the body’s inflammatory response
  - » Prevents biofilm formation



## Avenova® In Vitro Comparisons with Betadine

- Avenova has a comparable microbial spectrum to Betadine\*
- Covers some bacterial strains missed by Betadine, like *Serratia marcescens*\*
- Avenova onset of activity is twice as fast as Betadine (1 min vs 2 min)<sup>1</sup>
- Avenova remains active with a toxicity level 1000x lower than Betadine\*

*\* Antimicrobial Activity Comparison of Pure Hypochlorous Acid (0.01) with other Wound and Skin Cleansers at Non-Toxic Concentrations, Russell Hoon, Suriani Abdul Rani, Ramin Najafi, Lu Wang, Dmitri Debabov; SAWC Spring 2013 and WHD 2013*

*1 Klocek, M.S., Mammen, A., Dhaliwal, D., Kowalski, R. Time-Kill Comparison of Povidone Iodine to Hypochlorous Acid against Endophthalmitis Isolates of Staphylococci. ARVO Annual Meeting 2016 Abstract Number 5861*

## Acute Conjunctivitis and Antibiotic Use

- “Conjunctivitis is the most common cause of red or pink eye, but most (up to 80%) are viral.”
- “Topical antibiotics (for bacterial infection) provide only a very modest beneficial effect on clinical remission.”

Antibiotic Rx	Combo Rx
- OD’s – 44%	OD’s – 30%
- MD’s – 36%	MD’s – 23%
- Non Eye Dr’s – 60%	Non Eye Dr’s – 8%

- One-fifth of all Rx’s were for a combination antibiotic-steroid “which are contra-indicated in acute cases of conjunctivitis.” (Not True!)
- Use of AdenoPlus may reduce diagnostic uncertainty and increase comfort with deferring antibiotic therapy.

*Ophthalmology, August, 2017*

## Perspective on Posterior Vitreous Detachment

- Occurs mostly between ages 50 and 70 (peak incidence 62)
- No association with refractive error, except patients with -3.00D or more go to P.V.D. 5-10 years earlier
- 80-90% of breaks associated with P.V.D. are in the superior quadrants

### Acute PVD and Retinal Tears

- The rate of an acute retinal tear associated with an acute symptomatic PVD is about 8% at the initial visit, and 1.5% of eyes without a tear on the initial visit are found to have a tear on follow-up examination.

Ophthalmology, January 2018

### Treatment of Vitreous Floaters

- Treatment options:
  - » Live with them
  - » Vitrectomy
  - » Vitreolysis
- YAG laser – angle of focus can be changed to reach floaters; special vitreous lenses allow the laser beam to focus on floater
- Advantages: simple, noninvasive, no pain or discomfort
- Disadvantages: healthy eyes getting elective surgery, risk of retinal detachment, possibly worsening of symptoms
- Clear visualization of floaters key to successful treatment
- Treatment may require more than one laser session; symptomatic vitreous opacifications (SVO); only SVO's > 4mm from retina treated
- Patient decision on benefits vs risks *CRST, May 2016 (Stancich)*

### Malpractice Risks Regarding Retinal Detachments

- Uptick in legal claims for diagnostic errors
  - » Especially retinal detachments
- “And by far the most frequently missed diagnosis in our entire study was RD– nothing else came close.”
- 85% of these missed RD's presented with risk factors specific to RD
- “The primary pathogenic mechanism– and the biggest risk factor– for RD is PVD.”
- Comprehensive ophthalmologists (and optometrists) should have a low threshold for referral to a retinal subspecialist.”

Reference: EyeNet, April, 2018

### Phlyctenular Keratoconjunctivitis

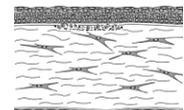
- nodular inflammation of paralimbal tissues
- mainly in children and young adults (females); allergic hypersensitivity response to some antigen to which the tissue has become sensitized (staphylococcal most common; TB rare)
- symptoms: photophobia and FB sensation (worse in corneal involvement)
- signs: pinkish-white elevations; +fl stain

### Thygeson's SPK

- Usually bilateral, punctate epithelial keratopathy of unknown etiology
- More common in women under 40; exacerbations and remissions over 1-2 decades possible
- Symptoms: fb sensation, lacrimation, and photophobia with minimal conjunctival injection
- Signs: coarsely scattered (4-20) intraepithelial granular opacities; stain lightly with fluorescein
- Tx: responds dramatically to topical steroids
- DDX with HSK, if unilateral Thygeson's eye:
  - » Mild injection
  - » Relatively abrupt onset
  - » Crushed bread crumb morphology

### Cross Section of Corneal Infiltrates

- These chemotactically attracted leukocytes migrate into the (usually peripheral) subepithelial tissues.
- If they are numerous enough or present long enough, epithelial compromise can occur which will manifest as a relatively small FI staining defect.
- At the stage depicted in this rendering, the bulbar conjunctiva is usually mildly injected.
- A topical antibiotic/steroid combination drug used QID for one week is the appropriate treatment.



## Differential Diagnosis of Corneal Ulcers vs. Infiltrates

### Ulcer (UK)

- ◆ Rare
- ◆ Usually painful
- ◆ Tend to be central
- ◆ 1 to 1 staining defect to lesion ratio
- ◆ Cells in anterior chamber
- ◆ Generalized conjunctival injection
- ◆ Usually solitary lesion
- ◆ Possible tear lake debris

### Infiltrate

- ◆ Common
- ◆ Mild pain
- ◆ Tend to be peripheral
- ◆ Staining defect size relatively small
- ◆ Rare cells in anterior chamber
- ◆ Sector skewed injection pattern
- ◆ Can be multiple lesions
- ◆ Clear tear lake

## Regarding Pupillary Abnormalities

- If there is:
  - No ptosis
  - No EOM dysfunction

Then it's nothing "bad" and a scan is not indicated

### *Consider:*

Adies, pharmacologic causation, or "discovered" physiologic anisocoria as probabilities

## Management of 3<sup>rd</sup> Nerve Palsy

- Pain vs no pain, pupil involvement, or not
  - Does not matter!
- All patients need emergent CTA or MRA
- Send straight to ED; not to an ophthalmologist
- However, about 95% of 3<sup>rd</sup> N. palsies are simply "microvascular," and not aneurysmal in nature

Foster PJ, et al. JAMA Ophthalmol 2017;135(3):203-4.

## Temporal (Giant Cell or Cranial) Arteritis

- Epidemiology: Generally Caucasians over age 60; fellow eye involved 75% within 2 wks without treatment
- Hx: HA, scalp tenderness, jaw claudication, malaise
- Ocular expressions: AION, CRAO/BRAO, EOM muscle palsies resulting in diplopia
- Medical Consultation with STAT ESR (results same day), CRP, fasting blood glucose, CBC
- If A-AION, then high dose I.V. methylprednisolone then oral taper
- Consider temporal artery biopsy and rheumatology consult for steroid management

## Epidemiological Perspective on GCA

- An idiopathic vasculitis of medium to large sized vessels of the head.
- Vision compromise occurs mostly from inflammatory posterior ciliary artery occlusion. CRAO is an uncommon expression.
- Average ESR was 70-80 mm/hr
- GCA results in permanent vision loss in about 10% of cases
- GCA predominately affects individuals of northern European descent.
- 20% of patients have no premonitory symptoms
- High dose steroids do little to regain lost vision, and are aimed mainly at preventing vision loss in the fellow eye

Turbert D. Ophthalmology, September, 2016

## New Developments in GCA

- "Like GCA, VZV also tends to affect the elderly as well as producing HA and scalp tenderness."
- Only a 1 cm length TAB is required
- "A TAB more than two weeks after the initiation of steroid therapy is still clinically valuable."
- "Most studies would favor using both ESR and CRP in combination to predict a positive TAB."
- Statins and NSAIDs lowered ESR by about 25%; CRP is not affected by these two drug classes.
- About 20% of patients with A-AION were "silent"; i.e. had no other cranial or systemic diseases.
- A pathologic trigger for GCA development is unknown.

Frohman L, et al. Surv Ophthalmol. 2016;61(4):400-421

## Tapering Oral Steroids in GCA

- The inflammation associated with GCA often requires many months of suppression therapy
- Oral steroids are initially required to aggressively suppress this idiopathic vasculitis
- Enhancing steroid tapering with a non-steroidal medicine should diminish steroid exposure
- Tocilizumab (Actemra) subcutaneously every two weeks significantly diminishes the need for enduring steroid therapy.
- This may be a “game changer” in the overall care and long-term management of GCA

*Stone JH, et al. N Engl J Med 2017;377:317-28*

## GCA: Role of ESR and CRP

- ESR clinical thresholds relative to GCA
  - » Men: Age ÷ 2 ; Women: Age + 10 ÷ 2
- ESR sensitivity (76-86%); CRP (97%); both (99%)
- When CRP is normal, but ESR is elevated, consider other disorders beyond GCA *Ophthalmology, October 2006*
- Best predictive lab studies: ESR, CRP, thrombocytosis
  - » ESR: Greater than 50-100 mm/hr (1.5 times)
  - » CRP: Greater than 2.45 mg/dl (5.3 times)
  - » Thrombocytosis: Greater than 400,000/uL (4.2 times)
- With all 3 tests positive: 8 times odds of (+) TAB

*Ophthalmology, June 2011*

## Finer Points Regarding GCA

- Positive TAB remains “gold standard”
- A 1cm section of the STA is ample
- TAB results still valid at 2 weeks post steroid treatment
- Both ESR and CRP are helpful in predicting a positive TAB
- Statins and NSAIDs cause ESR to be about 25% lower but CRP is unaffected by these drugs
- Significant anemia can cause a falsely high ESR

*Reference: Survey of Oph. Vol 61. July-Aug 2016*

## Alternative Oral Anticoagulants to Coumadin

- Direct thrombin inhibitor
  - » Pradaxa (dabigatran)
- Oral factor Xa inhibitor
  - » Xarelto (rivaroxaban)
  - » Eliquis (apixaban)
  - » Savaysa (edoxaban)

## Intraocular Bleeding with Novel Anticoagulants

- Dabigatran (Pradaxa®), rivaroxaban (Xarelto®), apixaban (Eliquis®), edoxaban (Lixiana®)
- Reduce the risk of intraocular bleeding by ~1/5 compared with warfarin (Coumadin®)
- Consider for patients at risk for proliferative diabetic retinopathy, the wet forms of ARMD, etc.

*Sun MT, et al. JAMA Ophthalmol, 2017;135(8):864-70*

## Efficacy of New Oral Anticoagulants Compared to Warfarin

- 50% fewer hemorrhagic strokes
- 25% more GI bleeds
- 10% lower all cause mortality

*Lancet, December, 2013*

## **Reversal Agents for Anticoagulants**

- Vitamin K quickly reverses warfarin, a vitamin K antagonist
- Newer anticoagulants: Pradaxa, Xarelto, Eliquis, and Savaysa
- Praxbind reverses Pradaxa
- The Xa-inhibitors; Xarelto, Eliquis, and Savaysa are inhibited by Andexanet within minutes
- Andexanet is a major enhancement to the clinical usefulness of these newer anticoagulants!

*Reference: NEJM. November 2015*

## **INR: International Normalized Ratio**

- A universally accepted measure of “coagulability”(clotting) behavior of blood in patients taking Coumadin® (warfarin).
- An INR of 1 is a normal, physiological clotting behavior.
- Target anticoaguable profile is an INR generally between 2 and 3.
- The higher the INR > 3, the thinner the blood thus increasing the risk of bleeding and hemorrhagic stroke.