

Eye Care Update – Part 2

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Financial Disclosure

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Glaucoma Drugs that Can Cause Corneal Edema

- Both CAIs and netarsudil (Rhopressa) can alter endothelial function resulting in corneal microcystic “reticular” epithelial edema, particularly after endothelial surgical procedures.
- Not all cases of corneal edema have endothelial dysfunction
- It may take days to a few months after initiation of therapy for corneal edema to become manifest.
- Such iatrogenic edema is a rare occurrence, but be attentive to such a possibility should corneal edema be a presentation.

JAMA Ophthalmology, August 2020

Timolol Eyedrops to Treat Migrane Headache

- Oral timolol or propranolol are effective in helping prevent migraine HAs, but are ineffective for treating acute HA.
- Oral beta blockers must be metabolized in the liver which is why they are not effective for acute treatment.
- However, “the use of eyedrops has the advantage of attaining peak plasma levels quickly at levels high enough to abort the acute migraine attacks effectively.”
- Instill 1-2 drops at the onset of the attack; 80% were significantly helped in 20 min.

JAMA Ophthalmol. Nov 2020

Anti-Viral Medicines

Topical

Trifluridine Viroptic
Ganciclovir Zirgan

Oral

Acyclovir Zovirax
Valacyclovir Valtrex
Famciclovir Famvir

- These are anti-herpetic drugs and are ineffective against the various adenoviral serotypes -

Topical Antiviral Options

Trifluridine

- Old drug
- Indiscriminate expression
- Potentially toxic
- More frequent dosing
- Refrigerate until opened
- Thimerisol preserved
- Solution (7.5 ml bottle)
- Viroptic and generic

Ganciclovir

- New drug
- Infected cell-specific
- Minimally toxic
- Less frequent dosing
- No refrigeration needed
- BAK preserved
- Gel (5 gram tube)
- Zirgan by B+L

Finer Points to Antiviral Prescribing

- For lactose intolerant patients: valacyclovir
- For children, use the oral suspension: acyclovir
- For patients over 65, famciclovir is recommended

Reference: AAO Guideline: Herpes Simplex Viral Keratitis: A Treatment Guideline- 2014 Appendix IV. Am. Acad. Ophthalmol.

Herpes Simplex Keratitis

- 90% of adults harbor the Herpes Virus
- Strain-specific expression of the disease
- Unilateral red eye with serous discharge
- Affected cornea has decreased sensitivity
- Males more commonly affected; recur more often
- 40% chance of recurrence within 5 years
- Fellow eye not at risk of involvement (1' and 2')
- Cause of recurrence: trauma, stress, adrenergic and prostaglandin eyedrops, fever, menstruation, climate, UV light
- Treatment: topical or systemic anti-viral

Valacyclovir vs. Acyclovir for Recurrent HSV

“One-year suppression therapy with oral valacyclovir (500-mg tablet daily) was shown to be as effective and as well-tolerated as acyclovir (400-mg tablet twice daily) in reducing the rate of recurrent ocular HSV disease.”

SOURCE: Miserocchi E, Modorati G, Galli L, Rama P. Efficacy of valacyclovir vs. acyclovir for the prevention of recurrent herpes simplex virus eye disease: A pilot study. *Am J Ophthalmol*, Oct. 2007

Study on Stromal HSK

- OD response rate, 6% - MD response rate 15%
- ALL: 95% treated epithelial keratitis correctly
- For stromal immune keratitis
 - 54% OD correct
 - 74% MD correct
 - 82% corneal subspecialist correct
- Correct = topical steroids with antiviral cover
- Correct use of oral antiviral prophylaxis for recurrences
 - 51% - OD, 60% - MD, 62% corneal subspecialist
- “Training” was most significant determining factor

Reference: *Letters – Arch. Oph.*, December 2010

Preventing HSV Disease Recurrences

- Patients being treated with oral antiviral therapy were 9 times less likely than untreated patients to develop recurrent keratitis
- Recurrence rates:
 - 27% at 1 year
 - 50% by 5 years
 - 57% by 10 years
 - 63% by 20 years
- Stromal disease is more likely to recur than epithelial disease
- Length of prophylaxis: Generally 5 disease-free years

Reference: *Arch. Oph.* January 2012

Shingrix Replaces 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.

Ophthalmology, Nov 2018

Reference:

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.”

Nov 2018

Reference: Ophthalmology,

Herpes Zoster Ophthalmicus

- Acute vesicular eruption of ophthalmic division of 5th cranial nerve
- Etiology: varicella-zoster virus; more common after 50 or in the immuno-compromised
- Symptoms: skin pain most common
- Ocular involvement in 50%
 - more common - zoster epithelial lesions, anterior uveitis, stromal keratitis, episcleritis
 - Tx: valacyclovir 1000mg tid for 1 wk; famciclovir 500 mg tid for 1 wk; acyclovir 800mg 5x d for 1 wk
 - If ocular involvement, treat with topical steroids

Primary HSV Infection

- Vesicular eruptions on the eyelid skin and/or eyelid margin
- Can be limited to the skin or can also result in follicular conjunctivitis and/or corneal epithelial disease
- Treatment:
 - PO ACV 400 mg 5 x D x 1W
 - PO Valtrex 500 mg tid x 1W
- Vesicles resolve without scarring

Non-ophthalmic steroid: ointment/cream/lotion

- Triamcinolone - moderate potency steroid
- Available in cream, ointment and lotion (0.5%, 0.1%, 0.025%)
- Our favorite: the 0.1% cream

Reference: Drug Facts and Comparisons

Systemic Prednisone

- Most common Rx'd systemic corticosteroid
- Common initial dosage 40-60 mg
- Available generically in both tablets and DosePaks (5 or 10 mg at 6 or 12 day course)
- Questions to ask before prescribing?
 - Diabetic?
 - Peptic Ulcer Disease?
 - Tuberculosis?
 - Pregnant?

Perspective on Oral Prednisolone

- Using oral prednisolone at 1,250 mg/day is equivalent to 1,000 mg of I.V. methylprednisolone sodium succinate (Solu-Medrol®) for 3 days in treating acute optic neuritis.
- “There was no significant difference in adverse events between the groups.”
- And,... we are concerned about using 40 – 60 mg/day!?!

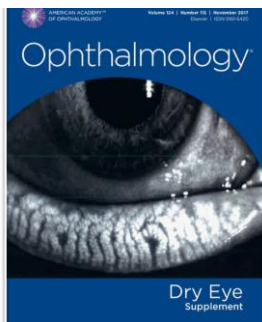
JAMA Neurology, June, 2018

Bilateral Periorbital Impetigo - Dermatitis

- Impetigo is a *Staph aureus* infection, often seen in patients with eczema
- Usually seen in children and young adults
- Can cause a secondary inflammatory dermatitis
- Can create cicatricial ectropion
- Tx with oral antibiotic and topical antibiotic/steroid or steroid ointment

Ophthalmology, June, 2018

Dry Eye Disease



- “Dry eye disease is a heterogeneous disorder of the ocular surface in which the common denominator is inflammation.”
- “Topical corticosteroids also play an important role in breaking the inflammatory cycle.” “Repeated short-term pulse therapy has produced a disease-free state for more than 1 year in a study of patients with Sjögren’s syndrome.”
- “Inflammation is one of the major targets in treating DED, and breaking the cycle of inflammation is crucial in improving symptoms. All patients DED deserve a trial of anti-inflammatory therapy at some point during their treatment.” “Corticosteroids are one of the most effective and rapid therapies available for suppressing inflammation on the ocular surface.”
- “Treatment of DED is based on minimizing inflammation and optimizing various components of the tear film.”

Discordance Between Symptoms and Signs

- Patients with chronic pain syndromes (CPSs) had 30% greater symptoms than signs.
- Important CPSs are irritable bowel syndrome, fibromyalgia, chronic pelvic pain and osteoarthritis.
- There is “growing evidence that part of the dry eye population may show signs of dysfunctional somatosensory pathways, indicating neuropathic ocular pain.”
- It is thought that “patients with atopy or allergy have a sensitized ocular surface because of inflammatory processes influencing corneal nerves, which can lead to symptoms of dry eye even when the homeostasis of the ocular surface is minimally compromised.”

Ophthalmology, March 2017

Dry Eye Diagnosis: “Symptoms”

- “Dry eye disease remains a largely symptomatic diagnosis, without a single diagnostic test.”

Reference: AJO, March 2015, P 470

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Ocular Surgery News, March 25, 2021

Topical Therapies for Ocular Surface Dryness

- Aqueous-based PF artificial tears did little or nothing to alleviate symptoms.
- Adding a topical steroid, signs and symptoms were improved.
- The majority of dry eye sufferers use AT’s, yet many still experience exacerbations of irritation and ocular surface disease in low-humidity environments.

Moore QL, et al. Am J Ophthalmol 2015;160(1):135-42

DED and Inflammation

- “A bedrock principle of modern DED care is that inflammation of the surface of the eye is responsible for tear dysfunction.”
- “Inflammation of the meibomian glands is a significant contributor to damage on the ocular surface.”
- M+T: It should be profoundly evident that loteprednol is the most ideal molecule available, providing both efficacy and safety. One month of therapy has been shown to eliminate ocular surface inflammation.

Ocular Surgery News August 25, 2020.

Steroids and Dry Eye Disease (DED)

- “Because chronic inflammation at the ocular surface plays an essential role in the pathogenesis of DED, topical steroids have been commonly used in these patients.”
- “Although the pathogenesis of DED is multifactorial and not fully understood, inflammation has been recognized as a key mechanism in its development and propagation.”

Am J Ophthalmol, June, 2018

Steroids in Dry Eye Disease

- “The original and still most effective treatment for pretty much all things dry eye is topical steroids.”
- “I predict that 2019 is year 1 in the Age of Steroids in DED.”
- M+T: This acknowledgement of excellence in patient care has been promoted by us since Lotemax came to market in 1998!

Ocular Surgery News, September 25, 2018

“Annual Anti-inflammatory Review”

- “As I predicted last year, steroids were big for all kinds of indications related to the ocular surface”
- “Once DED is diagnosed, the ASCRS protocol encourages aggressive, rapid-acting treatment that includes the use of steroids on the ocular surface. All kinds of loteprednol should see a bump in prescriptions written because of this.”

OSN September 25, 2019

Loteprednol Approved for Dry Eye

- October, 2020 marks the first FDA-approved steroid treatment for DED
- A 0.25% ophthalmic suspension formulation, however, only 2 or 3 shakes is necessary
- Unique “Mucus Penetrating” nanoparticle formulation enhances tear film residency time
- Approved for up to 2 weeks of QID therapy
- Can be “re-pulsed” as needed over time
- “Adverse events and IOP increases were comparable to those seen with vehicle.”
- Marketed by Kala as Eysuvis Ophthalmic Suspension

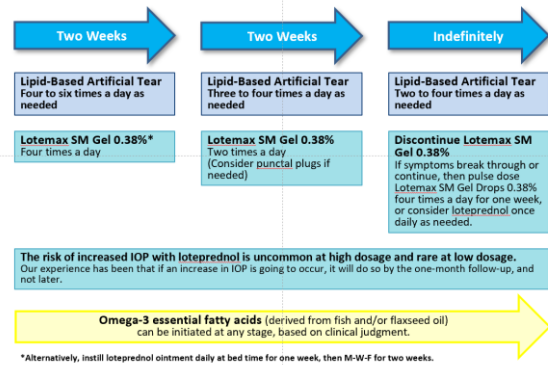
Literature Perspective on Steroids and

- **Elevated IOP** is more common with older steroids such as dexamethasone, prednisolone and fluorometholone, compared to newer steroids such as loteprednol, difluprednate or rimexolone.”
- A note about difluprednate: “Though the occurrence of increased IOP is about 3%, the IOP elevation may be significantly higher compared to the other newer steroids.” Only about 2% of patients experience “a clinically significant IOP increase” with loteprednol.
- “Post-operatively, loteprednol did not induce a significant IOP elevation and when used as a replacement for older steroids led to a significant IOP reduction in known steroid responders.”

Survey Ophthalmol. March/April 2020

Our Dry Eye Management Algorithm

All therapy – dry eye included – should be individualized to the patient. Here is our usual approach to dry eye management.



The risk of increased IOP with loteprednol is uncommon at high dosage and rare at low dosage. Our experience has been that if an increase in IOP is going to occur, it will do so by the one-month follow-up, and not later.

Korb's Lid Wiper Epitheliopathy

- “Consistently and accurately assessing LWE is fast becoming an important component of DED identification and treatment.”
- (You don't hear much about this because there is no drug or device - profit motive - to using LG dye!)
- We recommend generous application of LG dye, wait 3-4 minutes, and evert the lid.
- “Steroids can reduce para-inflammation from microtrauma of the shearing forces during blinks.”
- Lipid based artificial tear lubrication and Lotemax SM Q.I.D for two weeks is our typical approach.

Review of Optometry, November 15, 2020

Overview of Biological Agents

- These are medications that affect a biological process by modulating the immune response
- Interfere with function of cytokines which inhibit activation of T lymphocytes
- Cytokines function as mediators of inflammation and immune response; i.e. orchestration of leukocyte behavior
- Main targets of biologics: cytokines, interleukins, and tumor necrosis factor (TNF)

Regener-Eyes for DED

- First in class “biologic” eye drop
- Contains numerous anti-inflammatory cytokines and growth factors from placental-derived tissue
- Hyaluronic acid for lubrication
- Enhances the lipid layer
- Helps the body to regenerate itself
- Available as Regener-Eyes and Regener-Eyes Lite in a 3 ml sterile bottle
- See mydryeyes.org

Alternative Supplementation

- Orally administered omega-3 essential fatty acids
- May take 3 - 4 months to obtain a significant clinical effect
- Liquid formulations are available for those patients who have difficulty swallowing large capsules.

Role of Omega 3 EFA's in DED

- 30% reduction in the risk of DED for each gram consumed per day
- Recommend: about 1000mg of EPA and about 500mg of DHA per day
- Tear film BUT highly sensitive and specific
- Onset of benefits, including hyperemia; 30-60 days
- Loteprednol .5% QID x 2 weeks reduces ocular surface inflammation
- Krill oil appears to be slightly more effective than fish oil.

Reference: Oph. January 2017

Disturbing News on DED and Fish Oil



- Fish oil supplementation provides no benefit in treating DED!
- Conclusions: "Among patients with DED, those who were randomly assigned to receive supplements containing 3000mg of fish oil for 12 months did not have significantly better outcomes than those who were assigned to receive placebo."

NEJM, April, 2018

Benefits of Punctal Plugs

- "Plug placement resulted in greater than 50% improvement of symptoms, improvement in ocular-surface health, reduction in artificial tear use, and improved contact lens comfort in patients with dry eye."
- "The plugs are well tolerated, with only approximately 10% requiring removal for irritation."

Ophthalmology, August 2015

Melton-Thomas Recommendations for Dry Eye Treatment

Artificial Tears

- We recommend **Soothe XP** artificial tears. These tears contain mineral oil, which makes them more soothing for your eyes. Another good option is **Systane Balance** tears.
- Use these artificial tears 2-4 times a day (morning and evening are **critical**).

Warm Compresses

- Wet a washcloth with warm water and place it over your closed eyelids. Leave it there for 5-10 minutes; do this once per day.
- This will help stimulate the glands in your eyelids to produce more oil, helping to make better quality tears.

Blinking Exercises

- Close your eyes, squeeze them using your eyelid muscles, and release. Repeat these motions every 5 seconds for 1 minute. Do this one-minute exercise 4 times a day (breakfast, lunch, dinner, and bed times).
- These exercises will help your oil glands work better and will keep your eyes from drying out as much.

Fish Oil Supplements

- Take 2000 mg fish oil supplements every day.



The Benefits of Home-based "Warm Soaks"

- Heat application to the meibomian glands is a well-established therapeutic intervention
- All varieties of heat applications (warm soaks, etc.) fall short of ideal
- There is an evolving need to facilitate this therapeutically beneficial intervention
- EverTears technology is a self-contained, rapid-onset, heat-maintaining "pad" that patients can use to help maintain meibomian gland function at home
- OTC – Manufactured by THERMAMEDX

Lid Margin Debridement - Scaling

- "Hypothetically, early and frequent debridement-scaling of the Line of Marx (i.e., the muco-cutaneous junction) and lid margin could prevent or delay the cascade of increased osmolarity, tissue desiccation, and ultimately inflammation and tissue damage simply because of mechanical barriers to oil entering the tear film."
- "The single debridement-scaling procedure improved comfort and improved MG function."
- "There are significant benefits to a single D-S of the LOM and keratinized lid margin."

Cornea, December, 2013

MG Scraping in Treating DES

- "In the future, the health and maintenance of the MCJ and keratinized lid margin may be considered integral to routine eye care. This shift in our culture will involve improvements in our observation skills and also the willingness to incorporate novel techniques such as debridement-scaling of the MCJ and keratinized lid margin in our clinical practice."

Korb/Blackie. Cornea. December 2013

Hyperkeratinization and MGD

“Hyperkeratinization of the orifice and ductal epithelium, leading to meibomian gland obstruction, is considered the primary cause of meibomian gland disease. This directly results in decreased meibomian lipids on the ocular surface, resulting in an unstable tear film and evaporative dry eye conditions. Further, the increased internal pressure from the obstruction leads to atrophic changes and squamous metaplasia within the meibomian acini, causing a secondary hyposecretion.”

Survey of Ophthalmology, March-April 2015

Thermal Pulsation Treatment
CL Wearing Time

Increases

- “Conclusion: In SCL wearers with MGD, a single VTP treatment significantly improved mean meibomian gland function and significantly reduced dry eye signs and symptoms compared to an untreated control. The treatment increased mean comfortable lens wearing time by 4 hours (approximately doubling the pretreatment findings). This was sustained for up to 3 months post-treatment on average.”

Clinical Ophthalmology, Jan, 2018

In-office Procedure for Meibomian Gland Dysfunction

- Focused heat application followed by doctor-delivered meibomian gland expression is a critical intervention for moderate to advanced dry eye disease
- TearCare® (SightSciences) is an in-office procedure where heat strips are strategically placed over the eyelids to achieve optimum liquefaction of meibum
- Once liquefaction is quickly achieved, the doctor then properly expresses the meibum contents, thus allowing more physiological meibum to be produced.

Lumify (brimonidine 0.025%) Ophthalmic Solution

- FDA approved in December 2017 – OTC product
- Major upgrade to help the chronic red eye
- Venular constriction is the mechanism of action, therefore ...
- No rebound hyperemia
- Used once or twice a day PRN
- Marketed as Lumify OTC by Bausch & Lomb

Brimonidine Dermatologic Gel

- Used to address the erythema and flushing commonly expressed in facial and eyelid rosacea
- Causes microvascular vasoconstriction
- Comes in a 30 gram tube – applied once daily
- Provides a “somewhat effective” clinical response
- Available as a .33% gel (Mirvaso) by Gladerma

Reference: The Medical Letter, October 2013

Eyelid Cleansing Treatments for Blepharitis

- Study compared “dedicated eyelid cleanser to diluted baby shampoo”
- Cleansing was done bid for four weeks
- Conclusion: improvements occurred with both treatments. “However only the dedicated eyelid cleanser proved effective in reducing inflammation and was the preferred therapy.”

The Ocular Surface, October, 2017

Dermatologic Use of Oral Antibiotics

- Dermatologists prescribe more oral antibiotic courses per clinician than any other specialty, and many are prescribed for several months in duration.
- They are frequently used for acne, rosacea and other inflammatory conditions due to their potential anti-inflammatory properties.
- The most commonly prescribed antibiotics are:
 - Doxycycline hyclate 26%
 - Minocycline 26%
 - Cephalexin 20%

JAMA Dermatol. January 2019