

Melton-Thomas Clinical Grand Rounds (3)

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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

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

Key Issue:

When Should You Recommend Stopping Hydroxychloroquine Therapy...

A New App for Calculating Plaquenil Dosing

- About half of patients are overdosed
- Two somewhat competing approaches
 - » Calculating "Ideal Body Weight"
 - » Using "Actual Body Weight"
- This app known as "dose checker" blends the two approaches
- Put in the patient's height and weight and the proper weekly dose appears
- Proper dosing is the critical step in minimizing risk of Plaquenil maculopathy

JAMA Ophthalmology, February, 2018

Perspective on Poor Plaquenil Practice

- Based on "ideal body weight calculations", 50% of patients were overdosed (at 400 mg/day)
- At initial screening visits about 5% of patients received a 10-2 plus one objective test (usually a HD-OCT)
- Undertesting - - only a 10-2, or only an objective test (OCT, FAF, or mfERG) in about 30% of patients
- No testing occurred in 25% of Plaquenil patients!
- Amsler grid is of no value in HCQ testing, yet was done on 40% of patients.

AJO, September 2015

Rheumatologic Dosing of HCQ

- "Slightly more than ½ of all patients currently on treatment continue to receive excess doses."
- Toxicity can be up to 20% in patients taking HCQ after 20 years.
- "Our findings are particularly concerning given that choosing a proper starting dose is the single safest, simplest, and most cost-effective measure available."
- M+T: this is why it is vitally important for optometric physicians to know the science, then gently and authoritatively communicate with rheumatologists.
- "The calculation of a safe dose should be based on lean body mass, best estimated by the lesser of actual or ideal body weight."

Braslow RA, et al. Ophthalmology 2017;124(5): 604-8.

Key Issue:

When Do I Use A Steroid...

Steroids - General Principles

- Correct diagnosis is essential before prescribing
- Dose must be given on an individual basis
- Avoid prolonged use if possible
- Incidence of side-effects increases with time
- Steroids function by suppressing inflammation
- Aggressive short-term use is much wiser than undertreatment

A Clinical Guide to Corticosteroid Indications

- Iritis/iridocyclitis
- Episcleritis
- Inflammatory keratitis
- Post-operative care
- Ocular trauma
- Corneal infiltrates
- Ocular H₂O₂ inflammation
- Adenoviral infection
- Periocular contact dermatitis
- Eczematoid blepharitis

A Clinical Guide to Corticosteroid Indications

- Post-infectious inflammation
- x 1 month in inflammatory blepharitis
- Staph toxin tissue erosions
 - » angular blepharitis
 - » marginal corneal ulcers
 - » limbal infiltration
 - » microcystic corneal edema
 - » . . . and a host of other non-specific ocular inflammatory conditions

When NOT to use Steroids Alone

- Herpes Simplex Epithelial Keratitis
- Bacterial or fungal infection
- Large corneal epithelial defects
- Unsure of diagnosis, if not one of the above, consider a steroid
- If what is seen at the slit lamp defies precise diagnosis yet does not include one of these first three findings it is generally fine to treat with a steroid. In such cases, wisdom would dictate use of a combination drug, such as Zylet or TobraDex. This does not mean that therapy in such cases should always include a steroid; however, a steroid (preferably as a combination drug) could be rationally prescribed.

Exceptions to Steroid Guidelines: Using Antibiotic/Steroid Combinations

- Herpes Simplex Epithelial Keratitis - None (note that some cases of stromal HSK may require the judicious use of steroids)
- Bacterial Infections - If much secondary inflammation
- Epithelial Defects - If associated inflammation makes steroid suppression desirable, then use a combination drug
- Unsure - If a steroid is not contraindicated, then use of a combination drug is very acceptable.

Inveltys (loteprednol 1%) suspension

- "Treatment of post-operative inflammation and pain following ocular surgery"
- FDA-approved in August 2018
- Approved for BID administration
- Uses micro-particles to extend duration of efficacy
- Marketed by Kala Pharmaceuticals

Lotemax SM (loteprednol 0.38%) Gel

- "Treatment of post-operative inflammation and pain associated with ocular surgery"
- Approved for TID administration
- Delivers a submicron particle size for faster drug dissolution in tears
- Provides two times greater penetration to the aqueous humor compared to Lotemax Gel
- Lowest % of preservatives in a loteprednol formulation
- Marketed by B + L (5ml)

Long-Term FML Use After PKP

"In summary, we found that the prolonged use of 0.1% fluorometholone was beneficial for the prevention of rejection after PKP. Because no adverse consequences associated with the use of the eye drops were noted, we recommend continuing the use of low-dose corticosteroids, even in non-high-risk cases."

Reference: Oph, April 2012

M & T: *If such prolonged use of a ketone-based steroid is safe and effective, it would stand to reason that long-term use of loteprednol would be even safer. This has clear implications for long-term use in dry eye-related ocular surface inflammation.*

Children and Steroids

- "A tapering regimen of FML for ocular surface disease in children constitutes a safe anti-inflammatory treatment option to avoid steroid-induced glaucoma."
- "These patients may need prolonged treatment with FML to control the inflammation, a tapering regimen may help avoid steroid-induced glaucoma."
- No study had an increased IOP above 19mmHg.

(Reference: BJO, 2011, 95 (11), Pp 1531-1533)

M&T Commentary: *We would be much more comfortable using an ester-based corticosteroid such as loteprednol with these patients.*

Key Issue:

Will I Ever Get The Courage To Use A SYSTEMIC STEROID...

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?

From the "Uveitis Steroid Treatment Trial"

- "The finding that really surprises most clinicians is how little problem we encountered with systemic corticosteroids."
- "We found that the risk of side effects from systemic steroid therapy is very small, if it is done properly."

EyeNet, January 2012

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

Anti-inflammatory Effects of 0.1% Tacrolimus

- The topical calcineurin inhibitor, tacrolimus, has good anti-inflammatory properties.
- 0.1% tacrolimus eye drops can be highly effective in treating severe allergic conjunctival diseases.
- Tacrolimus eye drops often cause a stinging sensation or conjunctival redness, especially in the beginning of treatment of severely inflamed eyes. This can be avoided by topical steroid pretreatment.
- Tacrolimus eye drops did not have an immediate effect and required 1-2 weeks to be effective.
- In contrast, topical steroids are fast acting and can immediately relieve allergic symptoms. Although treatments eventually can be conducted without topical steroids, prompt relief of symptoms merits topical steroids.

Ophthalmology, March 2017

Key Issue:

Never Missing Glaucoma...

Optic Nerve Head Evaluation

- Cup depth is critical - Stereopsis!
- Are cup walls steep or sloping?
- Note rim translucency and vertical elongation of the cup
- Is the cup concentric with the disc, or is the cup displaced?
- Is the neuroretinal rim thinned more at certain clock hours than others? Especially look for any accentuated erosion of the inferotemporal or superotemporal regions.
- Is the disc generally pink, yellowish, or pale?

ISN'T

- Helpful diagnostic observation in ONH evaluation
- Normal neuroretinal rim anatomy follows the ISN'T rule
 - Inferior rim should be thickest
 - Superior rim is slightly less thick
 - Nasal rim is slightly less thick
 - Temporal rim should be the thinnest
- Most ONH's are round or slightly vertically oval
- ISN'T rule may not hold if ONH horizontally oval

Key Issue:

What's new in Glaucoma Treatment?

Compounding of Rx Glaucoma Meds

"Our compounded drugs are not FDA-approved as a whole, but each ingredient we use is FDA-approved. Since we are a compounding pharmacy, that is FDA-registered and inspected, we are able to compound these FDA-approved ingredients. Let me know if I need to explain a little clearer. If you have any other questions, please let me know. Thank you!"

Imprimis Pharmaceuticals

FDA Pregnancy Categories

- A- Controlled studies show no risk
- B- No evidence of risk in humans
 - » Either animal studies show risk, human studies do not; or if no human studies, animal studies negative
- C- Risk cannot be ruled out.
 - » Human studies lacking, and animal studies positive for fetal risk or lacking. Potential benefits may justify potential risks
- D- Positive evidence of risk post-marketing data show risk to fetus. If needed in life-threatening
 - » Investigational or situation of serious disease, drug may be acceptable if safer drugs cannot be used
- X- Contraindicated in pregnancy
 - » Fetal risk clearly outweighs any benefit to patient

Treating During Pregnancy

- 6.3 million pregnancies reported in US each year
- Pregnancy creates a natural reduction in IOP (19.6% reduction is normal; 24.4% decrease in OH)
- Past FDA Pregnancy Categories no longer apply for drugs approved after June 30, 2015; Doctor must now read the package inserts and analyze the safety data to make an informed decision.
- Until new drugs are approved, use the more familiar pregnancy category labeling
- In glaucoma, brimonidine only category B (avoid during lactation- linked to CNS depression)
- Consult patient's OB/GYN or PCP prior to treatment

Corneal Thickness (μm)	Correction Value
445	7
455	6
465	6
475	5
485	4
495	4
505	3
515	2
525	1
535	1
545	0
555	-1
565	-1
575	-2
585	-3
595	-4
605	-4
615	-5
625	-6
635	-6
645	-7

Correction values for applanation tonometer readings according to corneal thickness

Calculation based on data of Ehlers et al (1975)

Modified from Stodtmeister (1998)

Arithmetic mean of corneal thickness in healthy subjects: 545 μm (Doughty and Zaman 2000)

Correction values according to corneal thickness of 545 μm

Role of Self-IOP Measurements in Glaucoma Management

- Home tonometry – logical step in understanding and management of glaucoma
- Recent FDA approvals of devices
 - » Triggerfish (Sensimed) – contact lens
 - » ICARE Home (ICARE USA) – rebound tonometry requiring no anesthetic
- Home tonometry helpful in better understanding the IOP changes and to support future glaucoma management

News on “HOME” Tonometry

- “Up to 75% of individuals have peak IOP outside of office hours.”
- “Most patients (73%) were able to accurately measure their own IOP after a short training session. Self-tonometry was deemed comfortable and relatively easy to perform and has the potential to improve patient engagement in their own care.”
- “Patients with glaucoma may not only find self-monitoring of IOP acceptable, but also soon demand it.”

JAMA Ophthalmol, October, 2017

Prostaglandin Receptor Agonists

- Latanoprost (Xalatan and generic) 0.005%
- Travoprost (Travatan Z) 0.004%
- Bimatoprost (Lumigan) 0.01%
- Tafluprost (Zioptan) 0.0015%

Latanoprostene Bunod 0.024%

- FDA approved in November 2017
- First nitric oxide – donating prostaglandin
- One molecule – two mechanisms of action
 - » Enhances uveoscleral outflow
 - » Enhances trabecular meshwork outflow
- Reduces IOP by 6 – 7 mm Hg
- Preserved with 0.2% BAK
- Used once daily in the evening (6% red eyes)
- Comes in a 5 ml opaque bottle
- Refrigerate until opened
- Marketed as Vyzulta by Bausch & Lomb

Each Millimeter of IOP Reduction Matters

- “Our current understanding of the relationship between IOP lowering and glaucoma onset or progression translates to the effect of each mm Hg IOP reduction on the development of progression of visual field loss.”

de Moraes CG, et al. Survey Ophthalmol 2016;61(5):597-615

“Glaucoma Treatment: by the Highest Level of Evidence”

- The risk reduction could be about 19% per mm Hg, confirming results from the Early Manifest Glaucoma Trial and Canadian Glaucoma Study, and showing that IOP reduction is highly effective, and that every mm of pressure counts.
- These results should serve as a stimulus to the pharmaceutical industry to continue development of new and even more potent drugs.

Heijl, A. The Lancet, April 5, 2015

Perspective on IOP and Progression on Glaucomatous Optic Neuropathy

- “Progression was closely linked to the magnitude of the initial IOP reduction with treatment. The initial change in IOP (from baseline to the initial follow-up visit) was strongly associated with progression, with about a 10% lowering of the risk with each mm Hg of IOP reduction.”

Leske M, et al. Arch Ophthalmol, Jan 2003

- “Elevated IOP is a strong risk factor for glaucoma progression, with hazard ratio increasing by 11% for every 1 mm Hg of higher IOP”

Bengtsson B, et al. Ophthalmology, Feb 2007

Xelpros™ (0.005% latanoprost)

- Xelpros is non-BAK preserved latanoprost
- Preservative is 0.47% potassium sorbate
- (Zioptan® is the only preservative-free formulation of a prostaglandin)
- Not available in retail pharmacies
- Must be ordered through their contracted compounding pharmacies, and the requisite 3-month supply is shipped monthly directly to the patients
- See Xelpros.com (Sun Pharmaceuticals) for details
- Dosed once daily, exactly as any other latanoprost product

Rhopressa (netarsudil 0.02%)

- FDA approved in December 2017
- First rho kinase inhibitor
- MOA purported to be enhancement of conventional trabecular outflow
- Use once daily in the evening
- Reduces IOP about 4-5 mm Hg
- Preserved with 0.015% BAK
- Comes in a 2.5 ml bottle
- In phase III, 53% experienced red eyes
- Marketed by Aerie Pharmaceuticals

Rocklatan™ Ophthalmic Solution

- A combination of netarsudil 0.02% (Rhopressa) and latanoprost 0.005%
- First combination drug of a prostaglandin and a rho-kinase inhibitor
- Both ingredient drugs are “once daily” administration
- As with new drugs, coupons may be essential to achieve cost-effectiveness
- Conjunctival hyperemia (59%) may be a limiting factor
- Marketed by Aerie Pharmaceuticals

Key Issue:

After a prostaglandin, what's next?

After a Prostaglandin; What to Add

- Meta-analysis of studies regarding what drug to add to a prostaglandin
- Is it brimonidine, a beta-blocker, or a CAI?
- Conclusions: “All 3 classes are similarly effective in lowering mean diurnal IOP when used in combination with PGAs. Brimonidine is statistically less effective in reducing IOP at trough compared with the beta-blockers and CAI's.”
- Additional lowering of IOP was, on average, 2.5 to 3 mmHg for all 3.

Reference: Arch. Oph. July 2010

Contemporary Glaucoma Medication Flow

1st Tier: Prostaglandin q d or timolol q am

2nd Tier: Topical CAI or brimonidine

3rd Tier: Combigan, Cosopt, or Simbrinza

4th Tier: Pilocarpine
Oral CAI (preferably methazolamide)

Beta-Blockers as Second Line Therapy

References

- Angelo P. Tanna; Albert B. Lin. Medical Therapy for Glaucoma: What to Add After a Prostaglandin Analogs? *Curr Opin Ophthalmol.* 2015;26(2):116-120.
- Overview of Current Medications for Open-Angle Glaucoma (Supplement to *Glaucoma Today*, July/August 2016)

Neuroprotection

“Despite the long list of neuroprotective candidates, clinicians lack a proven neuroprotective agent with which to manage glaucoma.”

Glaucoma Today. November/December 2014.

Key Issue:

What About Marijuana For Glaucoma?

Marijuana For Glaucoma - NOT

- The American Academy of Ophthalmology does not recommend marijuana for the treatment of glaucoma
- No scientific evidence is found that marijuana is an effective long-term treatment for glaucoma, particularly when compared to the wide variety of prescription medication and surgical treatments available
- Initial studies in the 1970's reported that smoking marijuana did lower IOP for 3 to 4 hours but there is no evidence to date that proves it alters the long-term course of the disease
- Marijuana lowers blood pressure throughout the body, resulting in the potential to lower the blood flow to the optic nerve which can lead to vision loss
- No research exists to date that demonstrates that marijuana can deliver a level of efficacy compared to medicated eye drops or surgery.

Reference: “American Academy of Ophthalmology Reiterates Position That Marijuana Is Not Proven Treatment for Glaucoma”. www.ophtalmologyweb.com. July 3, 2014

Key Issue:

Itching and Burning: Is It Allergy or Dry Eye?

Allergic Conjunctivitis

Primary Symptoms	<ul style="list-style-type: none"> Itching that worsens with rubbing
Additional Symptoms	<ul style="list-style-type: none"> Burning sensation Diffused redness and inflammation Painless epiphora Symptoms present seasonally
Presentation & Differential Diagnosis	<ul style="list-style-type: none"> Inflamed lid margins Conjunctivitis Papillae Clear stringy discharge
Treatment	<ul style="list-style-type: none"> Cold compress and artificial tears for short-term treatment Immunotherapy Topical antihistamines/mast cell stabilizers Oral antihistamines may dry eyes Loteprednol
Choosing a CL	<ul style="list-style-type: none"> Daily disposables

A Fresh Look at Ocular Allergy

- Avoidance:**
- Bathe after being outdoors
 - Dust mite covers for pillows and mattresses
 - HEPA filters
- Treatments:**
- Chilled artificial tears
 - Cold compresses (frozen bag of peas or corn)
 - Alrex with glycerin moisturizer
 - Topical antihistamines selectively blocking the H₁ receptor to avoid exacerbating dry eye such as Bepreve or Lastacaft

Jackson MA. Start your drops: Allergy season has arrived. *Ocular Surgery News*, May 10, 2017.

Treatment Options - Ocular Allergy

- Artificial Tears
- Mild Vasoconstrictors
- Decongestant / Astringents
- Vasoconstrictor / Antihistamines
- Antihistamines
- Antihistamine / Mast Cell Stabilizers
- Mast Cell Stabilizers
- Non-steroidal Anti-inflammatories
- Mild Corticosteroids
- Systemic Antihistamines
- Potent Corticosteroids
- Homeopathic Formulations

Antihistamine/Mast Cell Stabilizer

- Highly selective H₁ receptor blockers with prolonged receptor binding
- Good mast cell stabilization
- All bid dosing, except Pataday and Lastacaft qd

Olopatadine	0.1%	(Patanol) (5 ml)
	0.2%	(Pataday) qd (2.5 ml)
	0.7%	(Pazeo) qd (2.5ml)
Bepotastine	1.5%	(Bepreve) (5, 10 ml)
Epinastine	0.05%	(Elastat and generic) 5 ml
Alcaftadine	0.25%	(Lastacaft) qd (3 ml)
Azelastine	0.05%	(Optivar and generic) (6 ml)
Ketotifen	0.025%	(generic and OTC)
		(Claritin Eye) (5 ml)
		(Zyrtec Itchy Eye) (5 ml)
		(Zaditor) (5 ml)
		(Alaway) (10 ml)
		(Refresh) (5ml)
		(TheraTears) (5 ml)

Cetirizine 0.24% ophthalmic solution

- Now Indicated for ocular itching associated with allergic conjunctivitis
- Instill 1 drop in each affected eye BID (8 hr apart)
- Adverse Effects:
 - Hyperemia (1-7%)
 - Instillation site pain (1-7%)
 - Reduced visual acuity (1-7%)
- Marketed by Nicox as Zerviate ophthalmic solution

Treatment of Ocular Allergies

Minimal	Mild	Moderate	Severe	
Antihistamine/ Mast Cell Stabilizer			Loteprednol	

Phthiriasis Palpebrarum

- Phthirus Pubis (crab louse) eyelid infestation
- Uncommon form of blepharitis
- Symptoms: intense itching (pruritus)
- Signs: nits (louse egg cases) and reddish sanguinofecal debris at base of eyelashes classic slit lamp findings
- Treatment
 - » Forceps to remove lice at slit lamp
 - » Standard lid scrubs and aggressive ointment to lid margins bid x 7 days
 - » Consult with primary care physician

Key Issue:

Treating That Stubborn GPC...

Intranasal Steroids for Ocular Symptoms in Allergic Rhinitis

- In a randomized trial, intranasal steroids relieved both nasal and ocular symptoms.
 - » Because intranasal steroids are the most effective medications for allergic rhinitis symptoms (especially congestion), guidelines recommend them as first-line agents for moderate-to-severe disease
 - » As many as 85% of patients with seasonal allergic rhinitis also have ocular symptoms
 - » For these patients, many clinicians prescribe oral antihistamines or ocular products rather than (or in addition to) intranasal steroids

Key Issue:

Does Breathing Help Dry Eyes?

Key Issue:

New Options in Caring for Dry Eye Disease

Global "Ophthalmology" Perspective on Dry Eye Disease

From a Comprehensive Supplement in Ophthalmology, November, 2017.

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.”
- “When meibomian glands function correctly, the lipids secreted reduce ocular surface water evaporation and prevent dry eye. When these glands are reduced, absent or dysfunctional, the impact on the ocular surface can be immense.”
- “Treatment of DED is based on minimizing inflammation and optimizing various components of the tear film.”

Dry Eye Disease

- “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.”
- “Omega-3 supplementation is a well-tolerated therapy to improve ocular surface health in nearly all forms of DED and is generally recommended to be used for all patients with no other medical contraindications.”

Discordance Between Symptoms and Signs

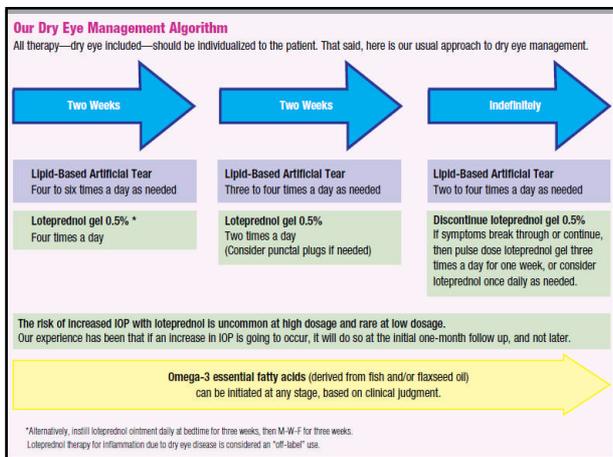
- Patients with chronic pain syndromes (CPSs) had 30% greater symptoms than signs.
- Important CPSs are irritable bowel syndrome, fibromyalgia, chronic pelvic pain and osteoarthritis.
- There is “growing evidence that part of the dry eye population may show signs of dysfunctional somatosensory pathways, 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

Expert Perspective on DED Inflammation

“It is now well understood that inflammation is one of the most important aspects of DED pathogenesis, and no matter the trigger, untreated or undertreated, established disease can lead to severe refractory disease. At this time, there are three topical prescription therapies available to treat inflammation in DED: corticosteroids, topical cyclosporine A and lifitegrast. Oral essential fatty acid supplementation and tetracycline-class antibiotics are also commonly prescribed for inflammatory ocular conditions, including DED.”

Sheppard J. Advanced Ocular Care, April 2017



Cyclosporine 0.05% Ophthalmic Emulsion

- Topical immunomodulator with anti-inflammatory effects – exact mechanisms unknown
- Indication: “to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation”
- Available in 0.4 ml unit dose vials by Allergan. Supplied in 30-vial tray.
- Dosage: one drop to affected eye(s) b.i.d. Usually takes 4-6 months to reach full therapeutic effect
- Concurrent treatment with ester-based steroid for the first 1-2 months may hasten results
- Available in multi-dose, non-preserved 5.5 ml bottle and unit-dose PF vials

Journal of the American Medical Association – Internal Medicine on Restasis

- A fundamental question: “Does Restasis Work?”
- Restasis has never been approved in the EU, Australia or New Zealand “due to insufficient evidence of efficacy.”
- “Although Canada approved Restasis, its National Technology Assessment Unit, unconvinced of meaningful benefit, recommended Canada not pay for it.”
- “Clinicians typically do not learn about new products from regulatory documents; they learn from commercially-sponsored, promotional efforts, such as detailing visits and events where food and beverages are provided.”
- It is so challenging to separate science from spin; these regulatory documents greatly illuminate reality and truth.

JAMA Internal Medicine, February, 2018

Xiidra (lifitegrast 5%)

- Only FDA-approved drug to treat both signs and symptoms of DED
- A lymphocyte function-associated antigen antagonist
- 5%, unit-dose (0.2ml), PF, foil-pouched solution
- Dosage is approximately every 12 hours for many months or years
- Takes 2-4 weeks to achieve clinical results
- Stored at room temperature – protect from light
- Side effects seen in 5-25% of patients include instillation site irritation, taste perversion (dysgeusia), and transient blurred vision
- Marketed as Xiidra by Shire (1 carton contains 12 foil packs holding 5 unit-dose containers)

Alternative Supplementation

- Orally administered omega-3 essential fatty acids
- May take 4-6 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

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.

Intranasal Neurostimulation

- FDA approved in April 2017
- Novel approach in dry eye treatment
- MOA: intranasal stimulation of tear production
- Triggers goblet cell degranulation
- Unknown: length, frequency of Tx sessions, efficacy, and duration of effect
- Marketed as TrueTear by Allergan

Neurostimulation and the Goblet Cell

- It is recognized that neural stimulation of the nasal mucosa plays a crucial role in stimulating homeostable aqueous tear production.
- Questions remaining:
 - » How long the increased aqueous or mucous tear volume lasts after a single application?
 - » How many treatment sessions per day are optimal?
- Numerous studies have found evidence of ocular surface inflammation.
- Such nasal neurostimulation might stimulate conjunctival goblet cell degranulation.
- Such an approach may be a unique feature of this therapy compared to other currently available treatments.

Gumas K, et al. Am J Ophthalmol 2017; 177:159-168

Summary

1. Global consensus – MGD is the leading cause of Dry Eye
 - Chronic and progressive
 - The sequelae can be catastrophic
2. Function and structure
 - A turning point for understanding MGD and dry eye and to practice both restorative treatment and prevention
3. Consider MGD first – the root cause of the vast majority of all dry eye
 - DE is complex due to the infinite sequelae of MGD
 - Understanding and treating MGD is now straightforward

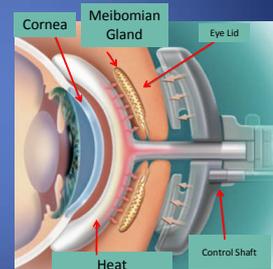
Progressive MGD

	Normal Function	Nonobvious MGD	Obvious MGD	Obvious MGD
Function				
Structure				

Thermal Pulsation



LIQUEFY, EXPRESS & EVACUATE
DUCTAL OBSTRUCTION AND GLAND CONTENTS



1. Apply controlled heat to the inner surfaces of both upper & lower lids
2. Simultaneously maintains pulsating pressure for 12 minutes

Pediatric DED and Risk Factors: Things to Ponder

- “Multi-screen” lifestyle – major risk factor
- Vegetarian and vegan lifestyle – insufficient consumption of Omega 3 EFA’s
- Meibography revealed that about 10% of grade school children had compromised meibomian glands.
- This compromise was directly correlated to the amount of time looking at screens
- “Evaporative DED associated with smartphone use is a lifestyle disease.”

Reference: OSN, January 25, 2016

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

Lid and Lash Hygiene

- Eye care products containing hypochlorous acid .01% / .02%
- Fast-acting cleanser for lids, lashes, periorbital skin with low toxicity
- Used for blepharitis and other conditions of eyelids or eyelashes which often cause inflammation and discomfort
- Effective against broad range of pathogens usually found on the lids and lashes
- Available in variety of formulations (solution, gel, spray)

Blepharitis Tx: Eyelid Cleanser vs Baby Shampoo

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Original Research

Randomized double-masked trial of eyelid cleansing treatments for blepharitis

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ABSTRACT

Purpose: To compare the efficacy of a dedicated eyelid cleanser and diluted baby shampoo in the management of blepharitis.

Methods: Forty-three participants with clinical blepharitis signs were enrolled in a prospective, randomized, double-masked, patient-eye trial. A dedicated eyelid cleanser (TheOculars® SteriLid™) was applied to the eyelids of one eye (randomized) and diluted baby shampoo (Johnson's® No More Tears®) to the fellow eye, twice daily for 4 weeks. Tear film parameters, ocular surface characteristics, symptomatology and cytology markers were analyzed at baseline and day 28.

Results: Baseline measurements did not differ between treatments (all $p > 0.05$). The eyelid cleanser was preferred over baby shampoo by the majority of participants ($p < 0.001$). Improvements in the tear lipid layer, inferior lid wiper epitheliopathy (IWE), cylindrical collarettes, and MMP-9 expression were limited to the dedicated eyelid cleanser (all $p < 0.05$), and a greater decrease in SANE symptoms score was also observed ($p = 0.04$). Meibomian gland capping and MUC5AC expression worsened with baby shampoo treatment (both $p < 0.05$). SPEED symptoms score, superior IWE, subconjunctival lash crusting, and trichiasis decreased significantly following application of both treatments (all $p < 0.05$), but did not differ between treatments (all $p > 0.05$).

Conclusions: Clinical improvements in blepharitis occurred with both treatments. However, only the dedicated eyelid cleanser proved effective in reducing ocular surface inflammation, and was the preferred therapy. Long term impact of decreased goblet cell function secondary to baby shampoo treatment requires further exploration.

Eyelid Cleansing Treatments for Blepharitis

- Study compared “dedicated eyelid cleanser to diluted baby shampoo”
- Cleaning 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

Intense Pulsed Light (IPL) Therapy

- IPL is a tx option for skin rosacea
- Studies show IPL reduces signs and symptoms of DED in patients with MGD
- Mechanism of action of IPL for DED not well understood; localized destruction of superficial blood vessels reduces inflammation associated with DED

Clinical Ophthalmology 2017:11

Doxycycline versus Azithromycin for MGD

- Patients (110) with MGD received oral azithromycin (500 mg day one, then 250 mg/d 4 days) vs one month oral doxycycline (200 mg/day) x 1 month
- After 2 months both groups significant improvement; percentage of clinical improvement better for azithromycin; less GI SE with azithromycin (4% vs 26%); azithromycin less expensive.

(Kahului MB et al. "Oral azithromycin versus doxycycline in meibomian gland dysfunction. Br J Ophthalmol. Feb 2015)

Review of Optometry 4-25-15

Dermatologists Prescribing for Acne

- Minocycline 44.4%
- Doxycycline 40.5%
- Azithromycin 3.2%

Reference: J Am Acad of Dermatology, October 2015

Key Issue:

The Changing Tide In Antibiotic Resistance...

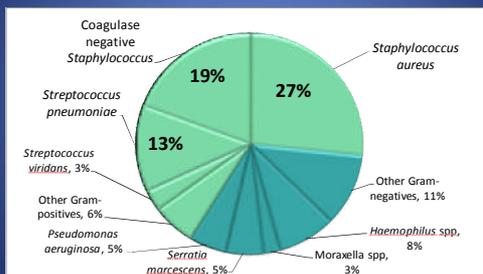
Antibiotic Resistance Monitoring in Ocular micRorganisms (ARMOR) Study

- Prospective, multicenter, longitudinal survey of antibiotic susceptibility trends
- Participating sites in the US include community hospitals, university hospitals, and ocular centers
- ARMOR isolates:
 - » *Staphylococcus aureus*
 - » Coagulase-negative staphylococci (CoNS)
 - » *Streptococcus pneumoniae*
 - » *Haemophilus influenzae*
 - » *Pseudomonas aeruginosa*

Asbell PA et al. JAMA Ophthalmol. 2015;1-10

Background

- *Staphylococcus aureus*, CoNS, *S. pneumoniae*, *P. aeruginosa*, *H. influenzae* are significant causes of ocular bacterial infections¹



¹ Kowalski RP, Dhaliwal DP. Expert Rev. Anti. Infect. Ther 2005;3(1):131-9. Figure adapted from Kowalski RP, Dhaliwal DP. Expert Rev. Anti. Infect. Ther 2005;3(1):131-9.

ARMOR Data - 2017

“This latest data demonstrate that while decreases in resistance are being observed, resistance to several commonly used antibiotics continues to be a challenge.” “Understanding these resistance trends can help eye care professionals ensure that their patients are matched with effective treatments and potentially avoid sight-threatening ocular infections.”

ARMOR, now in its tenth year, is the only nationwide study that monitors antimicrobial resistance in ocular infections.

Penny Asbell, MD, lead ARMOR study author, professor of Ophthalmology at Icahn School of Medicine at Mount Sinai, and director of the Cornea Service and Refractive Surgery Center at The Mount Sinai Hospital

Fluoroquinolone Non-susceptibility to Staphylococcal Epidermidis

- This Bascom Palmer study was done between 1995 and 2016

Ciprofloxacin 28% - 56%
Levofloxacin 17% - 56%
Moxifloxacin 22% - 57%

- Over half of *Staphylococcus epidermidis* pathogens were resistant, in vitro, to fluoroquinolones in 2016
- Conclusion: Prescribe based on science, not habit

Stringham JD, et al. JAMA Ophthalmol 2017;135(7):814-15

IMPORTANT DRUG WARNING

- Fluoroquinolones, including AVELOX®/CIPRO®, are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants.

Reference: HCNN (electronic health alerts) 10-22-08

- Fluoroquinolone therapy has been associated with possible tendinitis of the EOM's, resulting in diplopia.

Reference: Fraunfelder FW, Fraunfelder FT. Diplopia and fluorquinolones. Ophthalmology 2009; Jul 28 [Epub ahead of print]

Fluoroquinolones (Oral)

- Broad spectrum; especially effective for G- organisms (not effective against chlamydia)
- Resistant bacteria continue to emerge
- Side effects: mild GI, mild HA, dizziness
- Use conservatively in pregnancy and children when benefits outweigh risks; photosensitivity warning
- Avoid Ofloxacin and Levofloxacin with theophylline
- Avoid fluoroquinolones with Coumadin
- Cipro also available once daily; available generically
- Levofloxacin (Levaquin) has replaced Cipro as “gold standard” in oral fluoroquinolone therapy

The Numbers Behind Antibiotic Use

- “More than 8 in 10 Americans received antibiotic prescriptions in 2011
- “A total of 262.5 million courses of outpatient antibiotics were prescribed in 2011
- Rate of 842 prescriptions per 1000 persons
 - » For infants (age < 2 years), children (age 3-9) and older adults (age > 65) rates annually exceeded 1000 prescriptions per 1000 persons
 - » Amoxicillin was the most commonly prescribed antibiotic among children and teenagers
 - » Azithromycin was the antibiotic most commonly prescribed among young adults
 - » Women were almost twice as likely as men to receive antibiotics
- Antibiotic prescribing rates were considerably higher in the South
- Per-physician prescribing rates were highest among dermatologists, family practitioners and pediatricians”

Abigail Zuger, MD. Clin Infectious Diseases; Open Forum Infectious Diseases. May 2015.