What, Why, How about Dry Eye Disease Management

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Ocular Surface Disease

Dry Eye Disease Understanding has Changed

- 20 years since starting my first dry eye clinic
- 14 of those years were…. frustrating

Gender

- Sjogren’s: Dry eye is characterized by a *triatd* of dry eye, dry mouth, and associated autoimmune disorders
- Prevalence
  - 0.4%
  - 85% women

Predisposing factors

- Age
- Gender
- Environment
- Anterior Segment Disease
- Medications
- CL Wear
- Refractive or cataract surgery
- Systemic Disease

Prevalence of Dry Eye
(continued)

Prevalence by Age and Gender – WHS Study

![Prevalence Graph](image-url)
Environment

- Air conditioners or heaters
- Airline travel
- Winter months, allergy season
- Ceiling fan
- Exogenous irritants (smoking)
- Reading time
- Digital device use

DTS: Clinical Categories in 2006!

- Most common presentation: “No lid margin disease”
- Treatment decision based on severity level

Dysfunctional Tear Syndrome

No Lid Margin Disease  Altered Tear Distribution  Lid Margin Disease

Behrens et al, submitted

Anterior Blepharitis

Anterior Blepharitis?

OcuSoft Tea Tree Kit

- Contains Tea Tree Oil + Buckthorn seed oil
- Bland Ung QHS
- OcuSoft Lid Scrub Plus

BlephEx Treatment
Frothy / Foamy Tears = MGD

Key Components to MGD*

- Obstruction
- Inflammation
- Biofilm development
- Tear film alterations/instability

* Not present in all cases

Obstruction

- Lid margin debridement/scaling
- Commercial WC (e.g. Bruder, TranquilEyes etc.)
- Cold or manual expression
- Mechanical thermal pulsation

Obstruction: Debridement-Scaling

- Debridement-scaling of the line of Marx and keratinized lid margin improves MG function and reducing symptoms
- Korb DR1, Blackie CA. Debridement-scaling: a new procedure that increases Meibomian gland function and reduces dry eye symptoms. Cornea. 2013 Dec;32(12):1554-7

Warm Compress Effectiveness

- Olson MC1, Korb DR, Greiner JV. Increase in tear film lipid layer thickness following treatment with warm compresses in patients with meibomian gland dysfunction. Eye Contact Lens. 2003 Apr;29(2):96-9.
- Effective: Requires continuous heat and temperature
- Commercial compresses (e.g. Bruder) favored especially if they can provide hydration

Bruder Eye Hydrating Compress
Thermal Pulsation: LipiFlow

- Conclusion: Single 12 minute procedure statistically improved MG secretions, TFBUT and OSDI at 9 months.

Thermal Pulsation: LipiFlow

- Review of 31 peer-reviewed reports on vectored thermal pulsation therapy at the time of the search (eight manuscripts and 23 meeting abstracts).
- Effective: Optimal temperature for entire time, back surface, simultaneous expression.

BioFilm Development

- Lid hygiene products (e.g. Ocusoft Lid scrub plus or Sterilid etc.)
- Canister options seem to work well
- Surfactant and hypochlorus acid versions

Mechanical with surfactant cleaner (e.g. Blephex)

Inflammation and MGD

- Enríquez-de-Salamanca A1, Castellanos et al. Tear cytokine and chemokine analysis and clinical correlations in evaporative-type dry eye disease. Mol Vis. 2010 May 19;16:862-73

The Cycle of Inflammation

Importance of LipiFlow in managing meibomian gland dysfunction and improving dry eye symptoms.
Inflammation in MGD

- Combination agents & steroid agents
- Topical AzaSite
- Cyclosporine (Restasis)
- Omega fatty acids
- PO doxycycline or azithromycin

Clinical Research on Corticosteroids in MGD


Clinical Research on Cyclosporine and MGD

Prabhasawat P, Tesavibul N, Mahawong W. A randomized double-masked study of 0.05% cyclosporine ophthalmic emulsion in the treatment of meibomian gland dysfunction. Cornea. 2012 Dec;31(12):1386-93

Conclusions: OSDI, TFBUT, lid margin inflammation, meibomian gland expressibility, and tarsal injection showed significant improvement from baseline in group A (P<0.01, P<0.01, P<0.001, P<0.05, and P<0.001, respectively). In group B, only the OSDI improved significantly from baseline at 3 months (P=0.003).

Clinical Research on Cyclosporine and MGD

Rubin M, Rao S. Efficacy Topical Cyclosporine 0.05% in the Treatment of Posterior Blepharitis, Ocular Pharmacology and Therapeutics. Nov 2006: 22 (1)

Conclusions: Comparison of Cyclosporine to Tobradex for MGD after 12 weeks: greater improvements in Schirmer’s scores (P < 0.001) and TFBUT (P = 0.018) than tobramycin/dexamethasone

Mean improvement in meibomian gland secretion quality was significantly greater with cyclosporin (P = 0.015).
Higher percentage of patients in the cyclosporin treatment group had improvements in symptoms of blurred vision, burning, and itching and more cyclosporin-treated patients experienced resolution of lid telangiectasia
Mild MGD

- Hot/Warm compresses
- Lid hygiene
- Lipid based tears-mild/moderate
- Osmolarity lowering drops in moderate/severe

Moderate/Acute

- Tobradex ST
- Zylet
- AzaSite
- Tobradex generic
- Steroid drops or ung
  - (loteprednol preservative-free ung QhS)

Long Term

- Pulse dose medications periodically
- Restasis bid
- Essential fatty acids
  - EPA
  - DHA
  - GLA

Moderate/severe or not improving

- Add PO tetracycline
- Recommendation:
  - Doxycycline 50mg bid x 4-12 weeks then taper to qd
  - Doxycycline 20 mg bid x 4-12 weeks then taper to qd (periostat concern $$$)

Contraindications

- Pregnant or child bearing age
- Children

Tetracyclines

- Antibiotics inhibit bacterial protein synthesis by binding 30S ribosome
- Anti-inflammatory properties
  - decreases IL-1, TNF-α
  - decreases NO production
  - decreases HLA Class II antigen expression
  - decreases metalloproteinase production and activation
- Decrease symptoms and joint destruction in RA
Cautions

- Photosensitivity
- Chelates with dairy products, antacids etc.
- Minocycline may cause vestibular toxicity
- Number one drop-out reason?
- GI problems

Systemic medications

- Antihypertensives
- Anticholinergics
- Antidepressants
- Cardiac antiarrhythmic
- Oral contraceptives
- Hormone replacement therapy

Contact lens wear

- Schedule & Care
- Type of Lens
  - Daily Disposable
    - DT1, TruEye
  - Non-ionic, low water content, weekly disposable
    - Hydrogel Vision
  - SiHy 30 day
    - B&L Ultra

Refractive surgery

- Common for first 3-6 months
  - Neurotrophic
  - Goblet cell density
  - Tear flow

Mean Goblet Cell Density: Temporal Bulbar Conjunctiva

- *P < .001 vs baseline, tears, and CsA 6 weeks

- Significantly increased goblet cell density after 12 weeks of topical cyclosporine

Mean Goblet Cell Density: Inferior Bulbar Conjunctiva

- *P < .01 vs baseline and artificial tears

- Significantly increased goblet cell density after 6 and 12 weeks of topical cyclosporine
Systemic Disease

- Diabetes
- Rheumatoid Arthritis
  - Sjogren’s syndrome
- Thyroid Disease
- Dermatological: e.g. rosacea

Sjogren’s Syndrome

- Lymphocytic infiltration of lacrimal and salivary glands
- 0.4% prevalence
- Women > Men (younger women)
- Much lower androgen counts
- Treat underlying immune disorder

Which of these conditions are Sjogren’s patients 46x more likely to develop?

A. Leukemia  B. Lymphoma
C. Diabetes  D. Cardiac Arrythmia

Sjogren’s Syndrome

- Lymphocytic infiltration of lacrimal and salivary glands
- 5-8% incidence of B-cell non-Hodgkins Lymphoma
- 46.3x more often
  - Moutsopoulos HM et all

Medical Treatments: Secretagogues

- Salagen 5 mg
  - Pilocarpine tablets
  - Avoid in asthma patients, GI ulcer, acute iritis or narrow angles
- Evoxac 30 mg TID – saliva stimulating drug
  - Very effective with a lot less side effects

Symptoms of Dry Eye

- Burning
- Stinging
- Transient blur
- Dryness
- Photophobia
- Epiphora
- Blurred vision
- Contact lens intolerance
- Injection
- Foreign body sensation
- Grittiness
- Increased blink rate
Epiphora

- SLEX finding - Conjunctivochalasis or trichiasis
- Nasolacrimal sac obstruction
- Lid Laxity conditions - ectropion
- Dry Eye

Clinic-cytologic study of conjunctivochalasis and its relation to thyroid autoimmune diseases: prospective cohort study.

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Abstract

PURPOSE: To determine the prevalence of conjunctivochalasis in patients with immune thyroid diseases, to determine whether there is any association between the 2 diseases, and to determine cytologic study of conjunctivochalasis through the cytology impression test.

METHODS: A clinical prospective cohort study carried out by the External Diseases Department in the Ophthalmology Sector and the Thyroid Department in the Endocrinology Sector at Federal University of Sao Paulo (UNIFESP). The patients included were divided into 3 groups following these inclusion criteria: a control group of 25 patients without thyroid diseases, confirmed after clinical and laboratory examinations (thyroid hormones), or any other ocular diseases. The study group consisted of 31 patients with thyroid diseases, the diagnosis of which was confirmed by the Endocrinology Sector. The thyroidopathies included were autoimmune diseases but excluded non-autoimmune diseases. A protocol endorsed by the UNIFESP was followed, using

External examination

- Skin
- Eyelids
- Cranial nerve function
- Hands
Diagnostic Tests 2014

- Pt history
- Tear meniscus height
- Tear break-up
- NAFL Dye
- Rose Bengal or Lissamine Green
- Schirmer test - phenol thread test

Osmolarity

Hyperosmolarity and inter-eye differences increase with disease severity and return to normal with effective treatment.

Diagnostic Testing: Now/Future

1. Pt questionnaire- SPEED
2. TearLab osmolarity
3. Slit lamp examination
   1. CCH, anterior bleph, incomplete closure
4. MG Expression
5. NAFL Dye
   1. Tear meniscus height/TFBUT
   2. Corneal staining- late indicator
6. Meibography
7. Blink analysis

Tear Film Instability Increases With DED Severity

Osmolarity (mOsm/L)

- Normal
- Mild
- Moderate
- Severe

< 5 mOsm/L

Variability (±) mOsm/L

≥ 20 mOsm/L

Mild/Moderate Dry Eye

Severe Dry Eye

Corneal Staining
Other Diagnostic Tests of Value

- Light Seal Test -Transilluminate
- Bink analysis

Dr. i-Coach

A patented sensor and software package that can help users develop and maintain proper computer habits.

Features Include:

- Eye Fatigue Monitor (Blink Rate)
- User Distance Monitor
- Timer
- Seated Height Detector
- Environmental Light Detector

Eye Fatigue Monitor (Blink Rate): ala Fitbit

- Dr. i-Coach can efficiently track the eye region, detecting and counting user’s blinks.
- Blink rate data will be available in an easy to read chart for the use of the patient and their eye care professional.
- The Dr. i-Coach® software monitors and records the user's viewing time when there is any computer activity.
- After a viewing time between twenty to sixty minutes (pre-selected by the user), the program alerts the viewer and reminds them to take a break.

Treatment

- Based on distance, head-track localization, and screen tilt measured by an embedded gyroscope, Dr. i-Coach is able to determine if the user is seated at the proper height and reminds them to adjust accordingly.
Symptoms of DED but normal osmolarity, minimal other signs

- DED that is well controlled
- CL solutions related -PATH
- Mild allergic conjunctivitis
- EBMD- MDF dystrophy
- Pinguecula & early Pterygium
- Infection - e.g. conjunctivitis
- Anterior blepharitis
  - Demodex
- GPC
- Asthenopia - vertical, CI etc.
- Salzmann’s Nodular Degeneration
- Mild/mod conjunctivochalasis

Patient with epiphora will actually have osmolarity readings below normal or very low (i.e. < 280)

Treatment

- Emphasis chronic nature of the condition
- Eliminate exacerbating factors
  - smoking, air conditioner, meds.
- Drink 4-6 glasses of water per day
- Tear replacements

Role of AT’s

- Osmolarity lowering:
  - Blink Tears & TheraTears
- EBMD/corneal staining
  - FreshKote
- Lipid Deficient
  - Systane Balance, Soothe XP, Retaine MGD, Refresh Optive Advanced
- Aqueous deficient
  - Optive/Refresh, Systane Ultra
- Severe -------> Systane/Genteal gel or ung

Nutritional Supplements:

Essential fatty acids

- Omega fatty acids:
  - ALA- e.g. Flaxseed oil
  - EPA-DHA – e.g. Fish oils
  - GLA
  - Black Currant Seed Oil etc.

HydroEye (HE) Clinical

**Purpose:** Evaluate HE in postmenopausal women with moderate-severe KCS & tear dysfunction

**Dual Sites:** Virginia Eye Consultants & Baylor University

**Type:** Double-blind, placebo-controlled, randomized

**Duration:** 6 months

**Key Findings: Symptoms**

HydroEye® therapy significantly decreased the mean OSDI score over the treatment period ($p=0.004$), while the OSDI score was essentially unchanged in the placebo group;

At the end of 24 weeks, OSDI scores were significantly reduced in the HydroEye® group compared to placebo ($p=0.05$).
Targeted Treatments are KEY

- Treatments aimed at local inflammatory processes
  - Topical corticosteroids (Lotemax)
    - Effective anti-inflammatory agents
    - Site specific Steroids
  - Cyclosporin A (Restasis)

Dry Eye Disease—A Real Condition That Needs More Than a Palliative Solution

- “Dry eye is a disorder of the tear film due to tear deficiency or excessive tear evaporation which can cause damage to the interpalpebral ocular surface.”
- Artificial tears provide temporary palliative relief

Corticosteroids

- Bind to nuclear receptors that bind DNA and regulate gene expression
- Interfere with transcription regulators [e.g., AP-1 & NF-κB]
- Most inflammatory pathways
  - Cytokine production
  - Lipid mediators (PGs)
  - Cell adhesion molecules
  - Lymphocyte trafficking
  - Vascular permeability
- Ring modifications alter potency and membrane stabilizing effects

Steroids and Dry Eye

Symptomatic improvement in irritation symptoms in 83% and objective improvement (↓ redness, dye staining and tarsal papillae, ↑ FTC) in 80% of 70 patients treated for 2 weeks with non-preserved methylprednisolone

Prabhasawat & Tseng BJO 1998
Steroids and Dry Eye

- Moderate (43%) or complete (57%) relief of irritation symptoms accompanied by corneal FL staining and resolution of filamentary keratitis in 21 SS patients treated for 2 weeks with non-preserved methylprednisolone (Marsh & Pflugfelder 1999)
- Patients often have long lasting relief after 2-week pulse therapy

Sjögren’s Syndrome KCS

Steroids Effectively Treat KCS (Marsh Ophthalmology 1999)

How Does Restasis™ Work?

- Restasis™ prevents T-cell activation (Kunert et al., Arch Ophthalmol. 2000;118:1489)
  - Activated T cells produce inflammatory cytokines that result in:
    - Recruitment of more T cells (Stern et al, IOVS. 2002;43:2609)
Topical Cyclosporine

- Restasis Ophthalmic Emulsion (Allergan)
  - Useful in long-term management of inflammatory DES
  - BID dosage
  - Cyclosporine A (CsA) 0.05% in castor oil vehicle
- Mechanism of action:
  - Inhibits activation of inflammatory T-lymphocytes, and induces immune cell apoptosis, stimulating lacrimal gland tear production
  - 3-4 months to achieve clinically significant effect, 6 months for full therapeutic potential
  - 59% Patients achieved improvement from baseline Schirmer scores at 6 months
- Excellent safety profile

No Cyclosporine in Blood

- No detectable cyclosporine in blood of any RESTASIS® ophthalmic emulsion–treated patient
- Toxicity associated with systemic or oral cyclosporine was not observed with cyclosporine 0.05% ophthalmic emulsion
Options for Non-Responsive Patients

Punctal Occlusion

- May worsen certain conditions
  - Allergies
  - MGD
  - Inflammatory dry eye?
- Treat those conditions first then plug
- Ideal FIRST treatment option for:
  - Neurotrophic keratopathy
  - Post-LASIK dry eye
  - Lagophthalmos

Neurotrophic keratitis

Normal tears
- pH = 7.4
- Osmolality = 298
- EGF (ng/ml) = 0.2-3.0
- TGF-b (ng/ml) = 2-10
- Vitamin A (mg/ml) = 0.02
- Lysozyme (mg/ml) = 1.4
- Fibronectin (ug/ml) = 21

Autologous Serum
- pH = 7.4
- Osmolality = 296
- EGF (ng/ml) = 0.5
- TGF-b (ng/ml) = 6-33
- Vitamin A (mg/ml) = 46
- Lysozyme (mg/ml) = 6
- Fibronectin (ug/ml) = 205
- Hepatocyte GF, NGF, IGF-1, substance p, Complement, Fibroblast GF, c GRP, other Ig, etc.

LACRISERT® (hydroxypropyl cellulose ophthalmic insert)

LACRISERT is indicated in patients with moderate to severe dry eye syndromes (DES), including keratoconjunctivitis sicca.

LACRISERT is indicated especially in patients who remain symptomatic after an adequate trial of therapy with artificial tear solutions.

LACRISERT is also indicated for patients with exposure keratitis, decreased corneal sensitivity, and recurrent corneal erosions.

ProKera Amniotic Membrane

- Class II medical device comprising of CRYOTEK™ amniotic membrane into a thermoplastic ring set
- Combines the functionality of a symblepharon ring with the biologic actions of CRYOTEK™ amniotic membrane to create a unique treatment option for corneal and limbal wound healing
Clinical Evidence for PROKERA®

- A safe and effective method to promote healing of the corneal surface with minimal side effects 1
- Inhibits abnormal angiogenic processes and inflammation, thus promoting scarless healing1-7
- Stimulates healthy re-epithelialization of the corneal wound without sutures1,2,4,6,8
- Provides pain relief and reduces haze, resulting in improved visual acuity by a mean (SD) of 2.5 (2.6) Snellen lines 2


PROKERA® Insertion

- Set patient expectations! Inform the patient they may experience some initial stinging and foreign body sensation
- Apply topical anesthesia
- Rinse the PROKERA® a with a sterile solution (saline, BSS etc…)
- Hold the upper eyelid
- Ask the patient to look down
- Insert the PROKERA® into the superior fornix, preferably using your fingers to hold the ring
- Slide the PROKERA® under the lower eyelid

Scleral Lenses

Scleral lenses are large diameter gas permeable lenses that rest beyond the limits of the cornea and extend onto the sclera.
GLAUCOMA SIMILARITY

- Look at the structure and functioning of the MGs and ocular surface
- Multiple testing:
  - IOP = osmolarity
  - VF testing = corneal staining
  - OCT = meibomography/LipiView
  - MG expression = ONH examination

FUTURE: DENTAL MODEL

- Tooth Brush & Floss = Hydrating compress and lid hygiene products
- Scaling = Scaling/debridement of keratin
- Dental cleaning = mechanical pulsation or cleaning i.e. LipiFlow, Blephex etc.
- Dental X-rays = Meibography/Lipiview

Dry Eye Disease Conclusion:

- Understand the ramifications of not treating this disease
- The eyelids are key
- Be aggressive in your treatment and then reduce medications
- The single largest medical eyecare opportunity now and in the future

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