Expert Consensus in the Management of Ocular Surface Disease

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Ocular Surface Disease

Keratoconjunctivitis Sicca

- Irregular and Poorly Lubricated Corneal Surface
- Altered Barrier Function

Gender

- Sjogren’s: Dry eye is characterized by a triad of dry eye, dry mouth, and associated auto-immune disorders
- Prevalence
  - 0.4%
  - 85% women

Ocular Surface Disease Health

- Discuss the associated pathology of dry eye
- Discuss modalities of diagnosis, etiology and predisposing factors
- Latest research of dry eye treatments

Predisposing factors

- 
- 
- 
- 
- 
- 
- 

Prevalence of Dry Eye

(continued)

Prevalence by Age and Gender – WHS Study

[Bar chart showing prevalence by age and gender]
Environment

• Air conditioners or heaters
• Airline travel
• Winter months, allergy season
• Ceiling fan
• Exogenous irritants
• Reading time/Computer

Top intake causes of dry eye?

________________
________________ (more than moderate)
________________
________________
________________

Anterior Segment Disease

• Blepharitis/Meibomitis
• Patients are 2 x more likely to have dry eye symptoms
• Could be related to systemic conditions such as acne rosacea

DYSFUNCTIONAL TEAR SYNDROME

No Lid Margin Disease
Altered Tear Distribution
Lid Margin Disease

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

Anterior Blepharitis
Anterior Blepharitis

Paul Kersecki, OD
TSI

Anterior Blepharitis?

Cliradex

- Contains the active component of Tea Tree Oil (4–Terpineol)
- Preservative-free
- Safe for daily use
- Effectively cleans lashes, eyelids, and the face
- Refreshing menthol feeling
- Great for individuals seeking to improve overall eye and skin health
MGD

Frothy / Foamy Tears = MGD

Mild/Acute

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

- Self-closed colloidal particles
- Membranes composed of one or more lipid bilayer(s)
- The surfaces of bilayers are hydrophilic while the interior, which contain hydrocarbon chains, are hydrophobic
- Because of the different microenvironments in their structure, liposomes can encapsulate hydrophilic molecules
- Applications for lid disease but also drug delivery, diagnostics, computer vision syndrome and nutraceuticals

Moderate/Acute

- Tobra
dex ST
- Zylet
- AzaSite
- Tobra
dex
- Maxitrol

Long Term

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

Potential Chronic Changes

- Telangiectasia
- Dislocation of meibomian glands/gland atrophy
- Scarring

Moderate/severe or not improving

- Add PO tetracycline
- Recommendation:
  - Doxycycline 50mg bid x 4-8 weeks then taper to qd
  - Periostat (20 mg doxycycline) bid

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
Contraindications

• _______________________
• _______________________

Cautions

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

How to Minimize Stomach Problems with Tetracycline

1. Do not take the second pill (bid) before going to bed
2. Do not take pills with acidic beverages
3. Take pills with food (except a high dairy meal)
4.Prescribe the lowest dose available

Systemic medications

• Antihistamines
• Diuretics
• Antihypertensives
• Anticholinergics
• Antidepressants
• Cardiac antiarrhythmic
• Oral contraceptives
• Hormone replacement therapy

Contact lens wear

• Schedule & Care
• Type of Lens
• Daily Disposable
  • DT1
• Non-ionic, low water content, weekly disposable
  – Hydrogel Vision icuity

Tear Volume in Ocular Allergy Patients

![Graph showing tear volume reduction over days of treatment]
**Refractive surgery**

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

**Mean Goblet Cell Density:**

- Temporal Bulbar Conjonctiva
  - Significantly increased goblet cell density after 12 weeks of topical cyclosporine
  - *P < .001 vs baseline, tears, and CsA 6 weeks

- Inferior Bulbar Conjonctiva
  - Significantly increased goblet cell density after 6 and 12 weeks of topical cyclosporine
  - *P < .01 vs baseline and artificial tears

**Systemic Disease**

- __________________________
- __________________________
  - Sjogren’s syndrome
  - __________________________
  - Dermatological: Rosacea & Psoriasis

**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 Arrhythmia
Sjogren’s Syndrome

• Lymphocytic infiltration of lacrimal and salivary glands
• 5-8% incidence of
  —Moutsopoulos HM et al
• 46.3x more often

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
• Increased blink rate
• Foreign body sensation
• Grittiness

Epiphora

• ___________________________
  —
  ___________________________
  —
  ___________________________
  —
  ___________________________
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 2 groups: 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 nonautoimmune diseases. A protocol endorsed by the UNIFESP was followed, using clinical and ophthalmological history, biomicroscopy and impression cytology.

RESULTS: Fifty-two percent of patients without thyroid disease and 88% of patients with thyroid diseases presented with conjunctivochalasis. The risk ratio was 1.705 (Pr > chi(2) = 0.0038), indicating that there is an association between them. For the impression cytology in inferior bulbar conjunctiva, there was an association between the result of the impression cytology and conjunctivochalasis (Pearson chi(2) = 10.1190 Pr = 0.006).

CONCLUSION: The prevalence of conjunctivochalasis in patients with autoimmune thyroid diseases was 88%. Patients with autoimmune thyroidopathy presented higher percentages of conjunctivochalasis than the control group, confirming the association between them. The cytologic study showed the highest prevalence of abnormal surface features in eyes with conjunctivochalasis.

External examination

- Skin
- Eyelids
- Cranial nerve function
- Hands

Diagnostic Tests

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

- TearLab
- Osmolarity testing
- FDA approved
- 10 milli-microliters of tears
- Instant measurements of osmolarity in your clinic!

Treatment

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

Treatment – AT’s

- Blink Tears & Oasis Tears
- FreshKote
- Systane Balance or Refresh Optive Advanced
- Optive/Refresh
- Systane Ultra
- Genteal gel -----> Systane gel
- TheraTears

Before
FreshKote OS
After FreshKote
TID x 4 weeks OS

Nutritional Supplements:
Essential fatty acids

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

Autologous Serum

Patients blood is drawn
Centrifuge serum away from RBC
Serum contains various growth factors including epithelial growth factor
Mix with artificial tears
Patients doses 6 x per day
Most Eyebanks are now offering this service

Normal tears

<table>
<thead>
<tr>
<th>Autologous Serum</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH = 7.4</td>
</tr>
<tr>
<td>Osmolality = 296</td>
</tr>
<tr>
<td>EGF (ng/ml) = 0.2-3.0</td>
</tr>
<tr>
<td>TGF-β (ng/ml) = 2-10</td>
</tr>
<tr>
<td>Vitamin A (mg/ml) = 0.02</td>
</tr>
<tr>
<td>Lysozyme (mg/ml) = 1.4</td>
</tr>
<tr>
<td>Fibronectin (μg/ml) = 21</td>
</tr>
</tbody>
</table>

| pH = 7.4 |
| Osmolality = 296 |
| EGF (ng/ml) = 0.5 |
| TGF-β (ng/ml) = 6-33 |
| Vitamin A (mg/ml) = 46 |
| Lysozyme (mg/ml) = 6 |
| Fibronectin (μg/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®

- Class II medical device comprising 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 healing.\(^1\)\(^-\)\(^7\)
- Stimulates healthy re-epithelialization of the corneal wound without sutures.\(^1\)\(^-\)\(^4\)\(^-\)\(^6\)\(^-\)\(^8\)
- 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® 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 are large diameter gas permeable lenses that rest beyond the limits of the cornea and extend onto the sclera.

Scleral Lens Classification

- Classification designed by Dr. Rob Breece
- Corneo-Scleral
  - Corneal bearing and scleral touch
    - 12.9 - 13.5mm
    - Limited tear reservoir capacity
- Semi-Scleral
  - Corneal and scleral bearing
    - 13.6 - 14.9mm
- Mini-Scleral
  - Scleral bearing and minimal corneal clearance
    - 15.0 - 18.0mm
    - Somewhat limited tear reservoir capacity
Scleral Lens Classification
• Full Scleral
  – Scleral bearing and maximal corneal clearance
  • 18.1 - 24.0mm
  • Almost unlimited tear reservoir capacity

Scleral lenses: Contraindications
• Corneas with significant edema from reduced endothelial cell count

Punctal Occlusion
• May worsen certain conditions
  – __________________________
  – __________________________
  – __________________________
• Treat those conditions first then plug
• Ideal FIRST treatment option for:
  – __________________________
  – Post-LASIK dry eye
  – Lagophthalmos

Targeted Treatments
• 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

"Artificial tears are inadequate because they fail...to prevent progression of Dry Eye disease."
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

Steroid Treatment

- Loteprednol 0.2% (Alrex)
- Loteprednol 0.5% (Lotemax)
- Less side effects - M Abelson 88 patients 35 days
- IOP rise, secondary infection or PSC formation: 0%
- No reported cases of PCS cataract in over 36 Million prescriptions (IMS Health Data)

Ester vs. Ketone Steroids

- Ester Steroids are inactivated by naturally occurring esterases - less side effects
- Ketone Steroids are not inactivated and have propensity to remain in anterior chamber post breakdown as active metabolites

Ester vs. Ketone Steroids

Loteprednol → ester steroid
Prednisolone → ketone steroid
Fluorometholone
Dexamethasone
Medrysone
Rimexolone
Anti-inflammatory Therapy of KCS

Corticosteroids
- Improve signs and symptoms
- Improve tear clearance
- Normalize mucus production
- Often have sustained benefit after a 2 week pulse
- Bioengineered steroid loteprenol etabonate is effective

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)
    - More cytokine production
      (Pflugfelder et al., Curr Eye Res. 1999;19:201)

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
Expectations During the First 6 Months of Therapy

- 1 month
- 3 months
- 6 months

Patients notice an onset of benefit
Further increase in tear production
Significant improvement in tear production
Improvements are maintained with continuation of therapy

Cyclosporine
Restasis® Safety: Ocular Adverse Events (%)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>0.05% Cyclosporine</th>
<th>Vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burning upon instillation</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td>Stinging</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Discharge</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Foreign-body sensation</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Conjunctival hyperemia</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2</td>
<td>3.2</td>
</tr>
<tr>
<td>Visual disturbance</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Pain</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Epiphora</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>Data on File, Allergan, Inc.</td>
<td></td>
</tr>
</tbody>
</table>

Burning and stinging are the most important reasons that patients discontinue use of Restasis

- 17% of patients receiving Restasis experienced burning or stinging
  - Patients with dry eye have chronic ocular disease and are more sensitive to ocular insults
  - Patients with dry eye disease have anesthetic corneas
    - with return of tear function there is a return of corneal sensation, burning and stinging
  - Patients with dry eye are accustomed to treatment failure and are not willing to continue therapy which may make them feel temporarily

Topical Loteprednol Improves Patient Compliance and Restasis Efficacy

- Corticosteroids have been shown to improve tear production by controlling inflammation
- Corticosteroids decreases irritation associated with use of Restasis by 75%
- Recommend a mild corticosteroid such as loteprednol qid for two weeks and then bid for 2 weeks for patients who complain of irritation with Restasis, high maintenance patients, and patient who want more rapid relief

Progression of Dry Eye Disease

- Dry eye is a progressive, potentially irreversible disease
- Left untreated, the cycle of inflammation and dysfunction may cause permanent damage to the lacrimal gland

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

Please see slides 6 & 7 for important safety information.

2 Shepard, ASCRS 2005
3 Marsh, Pflugfelder. Ophthalmology 1999
Dry Eye Disease Conclusion:

- Inflammation at the root of the pathology as a cause or effect with osmolarity
- Numerous new treatment options that now make treating dry eye enjoyable
- Likely the most common condition we will see over the next two decades