Dry Eye: Etiology & Diagnosis

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A prudent question is one-half of wisdom
—Francis Bacon 1561-1626

English philosopher, statesman, scientist, lawyer, jurist and author
Proverb (Addendum)

A specialist is a doctor who trains his patients to become ill only during office hours—Anonymous

Lecture Outline

“WHAT IS DRY EYE?”
ETIOLOGIC CLASSIFICATION
  Aqueous deficient
  Evaporative
CONTRIBUTIONS
  Intrinsic/systemic
  Extrinsic/ environmental
DELICATE BALANCE OF HEALTHY TEARS
  Mucus, aqueous & lipid
Lecture Outline (cont)

DIAGNOSTIC TOOLS
  Questionnaires
  Old & New Testing Modalities
4 LEVELS OF DRY EYE SEVERITY (DEWS)
OVERVIEW OF TREATMENT STRATEGIES

Approach to the Dry Eye Patient
Classic Eye Care Practitioners’ Approach to Dry Eye Patient

Classic Approach to the Dry Eye Patient

Doctor Dry Eye Patient
Is Dry Eye Important?

- Dry eye hasn’t gotten any respect
- The dry eye corner was a very lonely place for a long time
- The “crabgrass” of eye care

UNTIL
- Studies began to show effect of dry eye on corneal topography and post cataract surgery visual acuity:
  - treating dry eye actually causes significant VA improvement
- Dry Eye is now the “hot dot” of eye care
  Source: Darrell White, MD

- Still skeptics  PROOF study Peter McDonnell MD med dir
New starlet of Eye Care: Dry Eye

Golden globe award

What is Dry Eye?
The Dry Eye Workshop (DEWS) 2007 Report

Dry Eye:
- multifactorial disease of the tears and ocular surface
  - tear film instability
  - potential damage to the ocular surface
  - increased osmolarity of the tear film
  - inflammation of the ocular surface
  - symptoms of discomfort, visual disturbance

DED is an immune mediated disorder

Healthy Tears:
The tear film and ocular surface:
--form an integrated physiologic unit
--surface epithelia and secretory glands linked via neural network.
Sensory-driven network
--regulates secretory activity in quantity and composition
--supports homeostasis of the system.

Lemp MA; AJO 2008
Sept;146(3):350-6
The tear film forms a metastable covering between blinks, subserving clear vision, maintains health and turnover of the ocular surface cells.

Lemp MA; AJO 2008 Sept;146(3):350-6
Disturbance of Intrinsic & Extrinsic Factors result in final common pathway at the tear film & ocular surface resulting in Dry Eye Disease

- **Intrinsic**, e.g.
  - increasing age
  - hormone balance
  - local & systemic autoimmune disease
  - systemic drugs

- **Extrinsic**, e.g.
  - topical meds
  - environmental stress
  - contact lens wear
  - refractive surgery

Lemp MA; AJO 2008 Sept;146(3):350-6

**Consequences of K. Sicca**

- mucus excess
- decreased luster
- punctate keratopathy
- filaments
- keratinization
- band keratopathy
And if there is any doubt, dry eye prevention & treatment is important...

**Cyclosporine study 0.05% (Restasis)**
- Over course of 1 year
  - 32% of AT patients progressed DE severity;
  - 6% on cyclosporine therapy

**PROOF study**
- Prospective 5 year: results in 2018
- Study of DES natural history
- >250 patients enrolled

McDonnell, Pflugfelder, Schiffman, et al. IOVS 2013;54 E-Abstract 4338

**Critical for good cataract and LASIK surgery outcomes**
Etiologic Classification of Dry Eye

- Aqueous Deficient
- Evaporative

DEWS Workshop Classification

Dry eye workshop 2007
Etiologic Classification of Dry Eye

**Aqueous Deficient**

- Sjogren’s Syndrome
  - Primary
  - Secondary
- Non-Sjogren’s
  - Lacrimal gland deficit
  - Reflex block (e.g., surgery)
  - Systemic drugs

Finds up to 30% of DED patients may have systemic disease
SJO TESTING
—New Diagnostic!

Myths of Sjögren’s

- “All Sjögren’s patients are identified and diagnosed”
- “There are only a few patients in my practice”
- “Nothing can be done for the patients if they are diagnosed”
- “Sjögren’s Syndrome does not have serious long-term consequences, it is just a nuisance”
Convergence of Facts

25 MM
Patients with Dry Eye

12.5 MM
will see their ECP

3 MM SS
patients still
undiagnosed

Impact of Sjögren’s

- Difficulty swallowing
- Heartburn, esophagitis
- Recurrent bronchitis, pneumonia, interstitial lung disease
- Arthritis, muscle pain
- Abnormal liver function tests, chronic fatigue
- Systemic lupus, autoimmune hepatitis, primary biliary cirrhosis
- Vaginal dryness, painful intercourse
- Musculoskeletal pain, myalgia, arthritis
- Cognitive symptoms (brain fog)
- Dry nose, recurrent rhinitis, nose bleeds
- Dry mouth, mouth ulcers, tooth decay; difficulty with chewing, speech, taste and smell
- Dry skin, vasculitis
- Sjögren’s phenomenon
- Gastrointestinal upset, dyspepsia
- Inflammatory bowel disease, pancreatitis
- Peripheral neuropathy, numbness and tingling in the extremities

Don’t forget Sjogren’s in Men

- Primary Sjogren’s in men represent about 10% of all primary SS patients.
- Men usually diagnosed decade later than women—61 vs 50 years (p<0.01).
- 92% report dry eye on presentation.
- Men more likely to present with more serious ocular complications than women.
- SS extraglandular manifestations more likely e.g. interstitial nephritis, vasculitis p=0.07.
- Men more likely negative for SS-A, SS-B, & ANA than women (36% vs 11% p=0.01).

AJO 2015 June 17 Mathews et al.

SjöDiagnostic Testing

Your patient’s dry eye symptoms may be rooted in a serious, progressive autoimmune disease.

Sjogren’s Syndrome affects an estimated 4 million people in the US, of which 3 million are undiagnosed. It is one of the 9 most common autoimmune diseases, affecting the exocrine glands, which are responsible for producing moisture.

It is estimated that 50% of patients are affected by Raynaud’s phenomenon.

Currently, there is an average delay of 6-7 years for patients to receive an accurate diagnosis for Sjogren’s Syndrome.

The early symptoms of Sjogren’s Syndrome commonly present as acute dry eye.

- Dry mouth is a common early symptom of Sjogren’s Syndrome and is present in 75% of patients.
- Other symptoms include swelling of the salivary glands, change in voice, intolerance to heat, and thin, dry hair.
- The onset of fatigue is often associated with Sjogren’s Syndrome.
- The estimated prevalence of Sjogren’s Syndrome is between 1 in 200 to 1 in 300 people.

As many as 1 in 10 dry eye patients also have Sjogren’s Syndrome.
Sjögren’s Syndrome Testing

Traditional testing

In the past, diagnosis of Sjögren’s Syndrome has been challenging, with limited tools and invasive procedures:

- Multiple tests need to be carried out to confirm a diagnosis.
- Salivary gland biopsy has traditionally been the gold standard for diagnosis even though it is invasive.
- Traditional biomarkers associated with Sjögren’s Syndrome may be less likely to detect the disease at an early stage.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSA (Ro)</td>
<td>Traditional</td>
</tr>
<tr>
<td>SSB (La)</td>
<td>Traditional</td>
</tr>
<tr>
<td>Antinuclear Antibody (ANA)</td>
<td>Traditional</td>
</tr>
<tr>
<td>Rheumatoid Factor (RF) Level (IgA, IgG, IgM)</td>
<td>Traditional</td>
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</table>

New early detection testing

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Type</th>
<th>Diagnostic Characteristics</th>
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<tbody>
<tr>
<td>SSA (Ro)</td>
<td>Traditional</td>
<td>Expressed in approximately 70% of patients and typically assessed later in the course of the disease than novel biomarkers.</td>
</tr>
<tr>
<td>SSB (La)</td>
<td>Traditional</td>
<td>Expressed less frequently than SSA and typically assessed later in the course of the disease than novel biomarkers.</td>
</tr>
<tr>
<td>Antinuclear Antibody (ANA) by HEP 2</td>
<td>Traditional</td>
<td>Expressed in about 70% of Sjögren’s Syndrome patients.</td>
</tr>
<tr>
<td>Rheumatoid Factor (RF) Level (IgA, IgG, IgM)</td>
<td>Traditional</td>
<td>Found in many rheumatic conditions but is not unique to Sjögren’s Syndrome.</td>
</tr>
<tr>
<td>Salivary Protein-1 (SP1, IgA, IgG, IgM)</td>
<td>Novel, proprietary</td>
<td>Provides high specificity and sensitivity for early Sjögren’s Syndrome.</td>
</tr>
<tr>
<td>Carbonic Anhydrase (CA-2, IgA, IgG, IgM)</td>
<td>Novel, proprietary</td>
<td>Offers additional sensitivity for an early diagnosis.</td>
</tr>
<tr>
<td>Parotid Secretory Protein (PSP, IgA, IgG, IgM)</td>
<td>Novel, proprietary</td>
<td>Expressed early in disease course.</td>
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</tbody>
</table>
SJÖ Diagnostic Test

- SJÖ testing recently acquired by Valeant (B&L)
- Testing becoming widely available by local major laboratories
- Now covered by insurance in many cases
- Cash price ~$1000 (US)

Turning to the Most Common Form of Dry Eye
DEWS Workshop Classification

Etiologic Classification of Dry Eye

Evaporative —

86% of Dry Eye Patients have Evaporative Component!
Etiologic Classification of Dry Eye

Evaporative—excessive water evaporation in presence of normal aqueous production

- **Intrinsic** (regulation of evaporation is directly affected)
  - Meibomian gland deficiency (posterior blepharitis)
  - Most common form

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**Table 4.** Meibomian gland diseases causing evaporative dry eye

<table>
<thead>
<tr>
<th>Category</th>
<th>Disease</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced number</td>
<td>Congenital deficiency, Acquired—MGD</td>
<td>Bron et al (2011)</td>
</tr>
<tr>
<td></td>
<td>Dystrophy, lymphedema syndrome</td>
<td>Brooks et al (2009)</td>
</tr>
<tr>
<td>Meiosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isosorescent</td>
<td>Meibomian sebaceous</td>
<td></td>
</tr>
<tr>
<td>Isosorescent MGD</td>
<td>Retinoid therapy</td>
<td>Mathers et al (2012)</td>
</tr>
<tr>
<td>Obstructive MGD</td>
<td>Primary or secondary</td>
<td>Bron et al (2015)</td>
</tr>
<tr>
<td>Recal or diffuse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple or cicatricial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atopic or inflammatory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local disease</td>
<td>Anterior blepharis</td>
<td></td>
</tr>
<tr>
<td>Systemic disease</td>
<td>Acne rosacea; seborrheic dermatitis; atopic; ichthyosis; parasitic</td>
<td>McCullough et al (2016)</td>
</tr>
<tr>
<td>Syndromes</td>
<td>Anhydronic atrophic dystrophy; ectodactyly syndrom; Turner syndrome</td>
<td>Rasmussen et al (2017)</td>
</tr>
<tr>
<td>Epinephrine (rabbit)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cicatricial MGD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local disease</td>
<td>Chemical burns; trachoma; pemphigoid; erythema multifactor; acne rosacea; VHC and AKC</td>
<td></td>
</tr>
</tbody>
</table>
Could eyelid tattooing induce Meibomian gland loss?

Your patient asks: “since I cannot wear makeup due to my dry eyes, can I have eyelid tattooing?”

Study: 10 tattoo subjects, 30 controls

- Distance between eyelid tattoo and MG’s measured; correl. Meibography & Meiboscore

Results:

- TBUT tattoo: 4.3 sec. vs 11.0 control p<0.001
- Fluorescein staining: worse tattoo (p<0.001)
- MG loss: 3.4 vs 0.9 control (p<0.001)

Lee, Kim, Hyon et al Cornea 2015; 34(7):750-755

Does eyelid tattooing induce Meibomian gland loss?

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Etiologic Classification of Dry Eye

Evaporative—excessive water evaporation in presence of normal aqueous production

- **Intrinsic** (regulation of evaporation is directly affected)
  - Meibomian gland deficiency (posterior blepharitis)
    - Most common form
    - Consider Demodex brevis (demodicosis)
      - Recurrent chalazia
  - Disorders of lid aperture
  - Low blink rate/ incomplete blinks
  - Drug action (e.g. retinoids such as Accutane)

Evaporative (cont)

- **Intrinsic** conditions (cont)
  - Meibomian oil deficiency
  - Low blink rate/ incomplete blinking
  - Wide lid aperture
  - Conjunctivochalasis
  - Aging/ low androgen pool
  - Systemic drugs
Etiologic Classification of Dry Eye

**Evaporative (cont)**

- **Conjunctivochalasis:**
  - Loss of Tenon’s capsule; redundant conj.
  - Reduces tear film reservoir

**Evaporative (cont)**

- **Conjunctivochalasis:**
  - Blue light and fluorescein shows redundant conjunctiva above lid margin
  - Tip of iceberg: shortens inferior fornix
  - Repair surgically
Etiologic Classification of Dry Eye

Evaporative (cont)

- Intrinsic conditions
  - Low blink rate/ incomplete blinking
  - Wide lid aperture
  - Aging
  - Conjunctivochalasis
  - Low androgen pool
  - Systemic drugs (antihistamines, B-blockers, antispasmodics, diuretics, psychotropic drugs)

Evaporative (cont)

- Extrinsic (increase evaporation by pathological effects on the ocular surface)
  - Vitamin A deficiency
    - Reduced goblet cells/ glycocalyx
Etiologic Classification of Dry Eye

**Evaporative (cont)**
- **Extrinsic (cont)**
  - Contact lens wear
    - (62% women; 40% men)
    - Aqueous tear film and lipid layer

**Evaporative (cont)**
- **Extrinsic (cont)**
  - Ocular surface disease (OSD)
    - e.g. **allergy**, inflammatory goblet cell reduction (mucin)
    - Topical preservatives;
      - BAK
    - drugs e.g. **glaucoma drugs** (OSD 30-70%), antimetabolites
      - inherent drug toxicity + preservative effect
Etiologic Classification of Dry Eye

**Evaporative (cont)**

- **Glaucoma Drugs**
  - Cross-sectional study 109 patients, 79 on topical preserved glaucoma medication
  - Results: Drug group
    - Shorter TBUT (p<0.03)
    - Greater fluorescein staining (p<0.001)
    - Higher impression cytology OSD score (p<0.001)
    - More drops caused worse FL staining & shorter TBUT
    - OSDI symptoms **NOT** different between groups


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**Evaporative (cont)**

- **Extrinsic/ environmental conditions**
  - Low relative humidity
  - High wind velocity
  - Occupational environment
  - Prolonged computer use
Etiologic Classification of Dry Eye

Evaporative (cont)

- Occupational environment
  - Prolonged computer/ cell use

Vision Council finds ~95% of Americans spend 2 or more hours daily on digital devices.

-- at risk for digital eye strain
-- redness, irritation or dry eyes, blurred vision, back & neck pain, headaches
-- concerns of blue light overexposure

CRST News Jan 2015

Healthy Tear Film Components
The Healthy Tear Film: A Delicate Balance
Lipid, aqueous & mucin components

Outer lipid layer prevents evaporation

- Secreted by meibomian glands

Image from *Dry Eye and Ocular Surface Disorders*, 2004

Lipid Secretion: Meibomian Glands

- The lipid layer
  - Restricts evaporation to 5-10% of tear flow
  - Facilitate tear film spreading over the ocular surface
  - Prevents skin FA’s from entering/disrupting tear film

Transillumination of meibomian glands

Transillumination image from Mathers; *Dry Eye and Ocular Surface Disorders*, 2004
The Healthy Tear Film: A Delicate Balance

- **Aqueous** component – a complex mixture of proteins, mucins, electrolytes
  - Secreted by main & accessory lacrimal glands

Aqueous Secretion: Lacrimal Glands

- Lacrimal glands secrete:
  - Aqueous component
  - Most tear proteins
- Similar architecture for main and accessory glands
- Androgens important for glandular homeostasis

(Sullivan et al., 1998)
The Healthy Tear Film: A Delicate Balance

Mucins

- Provide viscosity & stability during blink cycle (gel-like)
- Gel decreases in density toward tear film surface

Mucin Secretion: Goblet Cells

- 5-20% of conjunctival epithelial cells are mucin-producing goblet cells
- Soluble mucins - essential for viscosity of the normal tear film--Helps resist thin spots and tear break-up
- Tear film is somewhat like a mucin/aqueous gel
- Inflammation causes loss of goblet cells (apoptosis)
Healthy Tears

- A complex mixture of proteins, mucin, and electrolytes
- Antimicrobial proteins: Lysozyme, lactoferrin
- Growth factors & suppressors of inflammation: EGF, IL-1RA
- Soluble mucin 5AC secreted by goblet cells provides viscosity
  - Membrane-bound mucins 1 & 4 help stabilize tear film
- Electrolytes for proper osmolarity

Tears in Chronic Dry Eye (CDE)

- Lesser concentrations of many proteins in CDE
  - e.g. antimicrobial proteins
- Growth factor concentrations decreased
- Cytokine balance shifted, promotes inflammation
- Soluble mucin 5AC greatly decreased
  - Due to loss of goblet cells
  - Impacts viscosity of tear film
- Activated proteases
  - Degrade extracellular matrix & tight junctions
- Increased electrolytes/ hyperosmolar
Overall, Who Is Most Likely to Have Dry Eye? (abbreviated epidemiology)

- Women aged 50 or older
- Women using postmenopausal hormone replacement therapy
- Those with ocular comorbidities
- Contact lens wearers
- Users of artificial tears ≥ 3 times/day

Diagnosis

▲ Until recently, no reliable sensitive test to diagnose dry eyes
▲ If relatively severe, diagnosis made based on clinical exam +/- Schirmer’s testing
▲ Milder cases: establishment of diagnosis is often difficult and is based more on symptoms
   —Recent exceptions: MGD testing, Osmolarity & MMP-9?

Diagnosis: Questionnaires

▲ Currently, symptom questionnaires are among most repeatable of the commonly used diagnostic tests

▲ ~14 commonly used questionnaires
▲ Signs and symptoms often don’t correlate with moderate & severe disease
▲ Useful to monitor response to therapy
Diagnosis
Osaka study (2015)
672 Japanese office VDT users

- Found subjective happiness (subjective happiness scale) inversely correlated with dry eye symptoms score (Happy = fewer symptoms)
- Happiness Scale did not correlate with objective findings
- **Worst** symptoms with no objective findings found in unhappiest patients

PLoS One. 2015 Apr 1;10(4)

Diagnosis
Example symptom questionnaire:
**OSDI** for inflammatory dry eye
Diagnosis

Example symptom questionnaire:

**SPEED test**
--for evaporative tear film insufficiency

91 subject study of mild to moderate dry eye, correlating symptoms and common tests

- Aqueous deficiency tests (Phenol red thread, tear film break up time, slit lamp evaluation and impression cytology of goblet cells): no correlation with Dry Eye Questionnaire (McMonnie’s)

- Only lipid/mucous deficiency tests correlated with symptoms (MG pathology, reduced goblet cell density and TBUT correlated with Dry eye questionnaire)

Moore, Graham, Goodall et al Br J Ophthalmo 2009:93:66-72
Diagnosis Questionnaires caveat

- Recent studies have shown <60% of DED subjects with objective dry eye have symptoms
- Using symptoms alone likely to miss significant % of patients with DED, particularly with early/mild disease (e.g. anticipating cataract, refractive sx)


Common Tests for Dry Eye
Diagnosis: common tests

- Fluorescein staining
  - Conjunctival staining in milder cases
  - Corneal staining in more severe cases

- Deep yellow filter (Wratten #12)
- Evaluate after 1-2 minutes to detect late staining
Diagnosis: common tests

- Fluorescein staining
  - Conjunctival staining in milder cases
  - Corneal staining in more severe cases
  - Deep yellow filter (Wratten #12)
  - Evaluate after 1-2 minutes to detect late staining
  - Look for conjunctivochalasis folds

- Tear breakup time
  - Good aid for diagnosing meibomian gland dysfunction in presence of adequate aqueous layer
  - Fluorescein instilled, blink several times to distribute
  - Do before any anesthetic administration
  - Patient looks straight ahead without blinking
Diagnosis: Other tests

- **Fluorescein Dilution/Disappearance**
  - Measures decrease of fluorescence by production of new tears
  - Drop fluorescein instilled and fluorescence measured over time with stopwatch or photometer
  - Confounded by punctal occlusion

Diagnosis: Common tests

- **Tear breakup time**
  - Observe with cobalt blue light for black islands or streaks in the green film
  - <10 seconds abnormal
Diagnosis: common tests

- Rose bengal or lissamine green staining
  - Stains cells lacking protection by precorneal tear film and mucus
  - Interpalpebral pattern on conjunctiva and cornea

Milder cases staining limited to the conjunctiva.

Diagnosis: common tests

- Rose bengal or lissamine green staining
  - LG is more comfortable
  - Severest cases: most of cornea stains; mucus filaments may be present; SLK-like staining
Diagnosis: common tests

Schirmer's Testing (1903)

Schirmer's I
- Measures total reflex and basic tear secretion
- Unanesthetized
- Should not be <10 mm

Basic Secretion Test
- Instill topical anesthetic (wait 3-4 minutes)
- Dry cul-de-sac
- Insert Schirmer strips
- Wait 5 minutes
- Abnormal: <3mm
- False negatives frequent due to incomplete anesthesia
Diagnosis: common tests

Schirmer’s Testing

- Schirmer’s II (measures reflex secretion)
  - Rarely used
  - Instill topical anesthetic
  - Rub nasal mucosa with cotton swab
  - Measure wetting after 2 minutes
  - Wetting <15 mm = failure of reflex secretion

Phenol red thread test

- Less invasive
- 70mm cotton thread
- Wetting with tears 15 seconds
- Changes yellow red
- 9-20mm normal
Less Used Tests for Dry Eye

- Tear lysozyme
- Tear lactoferrin
- Impression cytology (conjunctival)
- Tear film osmolality
Newer Tests for Dry Eye

- Tear Film Osmolarity
- Tear Film Thickness
- MMP-9
- MGD Analysis
  - Physical inspection
  - Transillumination
  - Blink Analysis--videography
  - Meibomography
- MG expressibility (Korb MGE)
- Tear film lipid layer thickness--interferometry
Diagnosis: Newer tests

- Tear Film Osmolarity
  - Relatively sensitive for diagnosis
  - Tear Lab

DEWS Definition of Dry Eye Disease

Dry eye is a multifactorial disease of the tears and ocular surface... It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.

Testing for osmolarity is a good place to start

Note: the definition was updated 2 years prior to TearLab approval and based on 40+ years of research using tear osmometers requiring 500 to 1000 times the volume now needed (50 nanoliter sample)

Two Numbers Crucial to Understand Osmolarity

The MAXIMUM of the two eyes:
- Tears higher than 300 mOsm/L demonstrate loss of homeostasis and likely become pathogenic > 308.

The DIFFERENCE b/w two eyes:
- This shows the stability of the tear film. Normal tears are stable and < 300 mOsm/L bilaterally. A difference of < 8 mOsm/L is a hallmark of tear instability.

Non-DED Patients are Low and Stable - DED Patients are Elevated and Unstable

<table>
<thead>
<tr>
<th></th>
<th>Mild/Moderate Dry Eye Patient OSDI = 22.92</th>
<th>Normal Patient OSDI = 4.17</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right Eye</td>
<td>Left Eye</td>
</tr>
<tr>
<td>Day 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 min</td>
<td>311</td>
<td>326</td>
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<tr>
<td>2 min</td>
<td>304</td>
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<td>3 min</td>
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<td>308</td>
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<tr>
<td>4 min</td>
<td>337</td>
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<td>Day 2</td>
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<td>1 min</td>
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<tr>
<td>Mean</td>
<td>313</td>
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<tr>
<td>Stddev</td>
<td>11.8</td>
<td>11.5</td>
</tr>
</tbody>
</table>

Hyperosmolarity-Induced Apoptosis in Human Corneal Epithelial Cells Is Mediated by Cytochrome c and MAPK Pathways

Lihui Luo, MD,*† De-Quan Li, MD, PhD,* and Stephen C. Pflugfelder, MD*

Hyperosmolarity Upregulates EMMPRIN/MMP-9

High Osmolarity Increases EMMPRIN Expression in Human Corneal Epithelial Cells and Is Associated with an Increase in MMP-9 and a Loss of Epithelial Cell–Cell Junctions

Eric Huet,1° Benoit Yelles,2° Jean Delahaye,2° Samia Mounah,3‚ Virginia Pouilles Exadaktylos,1° Magali Taton-Bosc,1° Karin Kollmar,1° Serge Doin,1° Christophe Baudoz,2° Suzan Menezo,1°, and Eric E. Gahbauer1°

Cell remodeling, spk, surgery, ulceration

Hyperosmolarity Upregulates
--inflammatory cytokines
e.g. interleukins, metalloproteinases
--cycle of inflammation with apoptosis,
T-cell infiltration
--symptoms of dryness, irritation

Why Measure Tear Osmolarity?

Measuring osmolarity allows us to evaluate an actual **physiologic marker**
rather than a “sign” of the disease such as staining or tear break up time.

Like BP or serum glucose!
Abstract Title: Measuring Tear Film Osmolarity in Dry Eye Disease: A Review of the Literature
Christopher J. Rapuano, Rick Potvin (ASCRS 2015 Poster)

- Purpose: To analyze the role of objectively measuring tear film osmolarity in the diagnosis of dry eye disease, based on a review of the peer-reviewed literature.

- Methods: A literature search of all peer-reviewed articles associated with tear film osmolarity was conducted. Identified studies were graded into four categories: very low, low, moderate and high quality using the Grading of Recommendations Assessment, Development and Evaluation (GRADE)

- Results: 164 peer-reviewed study articles relevant to tear osmolarity and dry eye disease were identified. Of these, 72% indicated that tear film osmolarity was a useful diagnostic tool, while 7% suggested no utility to the test. Thirty percent of studies were rated as ‘moderate’ to ‘high’ quality based on study design. In this subgroup 73% supported the use of objective tear osmolarity measurement in dry eye diagnosis, 18% were neutral regarding the test and 10% suggested no utility.

- Conclusion: Tear film osmolarity has been identified as a central mechanism related to dry eye disease by the Dry Eye Workshop (DEWS) report. Peer-reviewed literature indicates that an objective evaluation of tear film osmolarity is valuable in the diagnosis of dry eye disease.

Tear Osmolarity: various studies

[Graphs showing osmolarity distributions for normal and dry eye conditions]
Tear Osmolarity: various studies

- What is the value of incorporating tear film measurement in assessing patient response to therapy in DED?
  - Single Institution study
  - 186 patients w/ DED
  - 2 visits: Tear Osm (Tear Lab) vs OSDI symptoms & fluorescein staining (mod Oxford scheme)

**Results**

- Fluorescein staining and symptoms modest correlation
- No correlation between change in OSM and symptoms

**Change in Tear OSM didn’t correlate significantly with changes in symptoms or corneal fluorescein staining between 2 visits**

Amparo, Dana et al AJO 2013: Sept 20 Epub

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Tear Osmolarity: various studies

Recent NHS (UK) study:

- 596 patients
  - Osm: highest positive *predictive value* of dry eye disease compared with other routine diagnostic tests (no Schirmer’s testing)
  - % DED by Osm 72.3%, in good agreement with DEWS scores (78%)

Besides the science, why Measure Tear Osmolarity?

*Patients may not think they have dry eye (e.g. down-regulated nerves).*

Osm = Objective number

- “This test shows that the Osm of your tear film is XX points above normal which indicates you have dry eye”—end of discussion
- Patients become aware of this number as something they want to work to lower, just like blood pressure or cholesterol levels
- Encourages compliance

M. McDonald, MD

Confounding variables of tear film osmolarity

- Time from most recent eye drops (2 h minimum)
- Environmental conditions
- Patient just drive to clinic?
- Other disease process e.g. allergy, blepharitis
- Blepharitis average Osm approaches 305 cut off --304 mOsm/L  *JAMA Ophthalmol 2015 Mar 26*
- Dry eye variability of 8 mOsm is typical; between visits—makes it hard to interpret response to therapy
Tear Osmolarity Can Be Used To Follow The Response To Treatment

- Objective way to determine if patient is responding to treatment
- Do at each follow up visit, like BP measurement
- If Osm improving, can reassure patient they are improving even if symptoms (or signs) haven’t improved yet
- Don’t rely on single day’s measurement

DED Can Affect Surgical Outcomes
Hyperosmolarity Can Decrease Visual Acuity and/or Quality of Vision including post-operatively

DED frequent cause of failure of premium lenses

Osm & Contact Lenses

- Diagnosing hyperosmolarity in potential contact lens patients, particularly past failed CL wear can signal need for aggressive therapy with Omega 3’s, MGD TX, plugs, Restasis…

- Once the hyperosmolarity is controlled, patients can be more likely to wear contacts successfully

- Studies are now showing hyperosmolarity responds well with Omega 3 supplements @ 2 months and this can be monitored over time

- Punctal occlusion has been shown in studies to reduce osmolarity in patients NOT having significant inflammation
Newer Tests for Dry Eye

- Tear Film Osmolarity
- Tear Film Thickness
- MMP-9
- MGD Analysis
  - Physical inspection
  - Transillumination
  - Blink Analysis—videography
  - Meibomography
  - MG expressibility (Korb MGE)
- Tear film lipid layer thickness—interferometry

Diagnosis: Other tests

- Tear Film thickness
- Corneal topography
- O.C.T.

Tear film thickness correlated w/ subjective symptoms Schmidt et al IOVS 2015 Feb 3:54(3):1467-72
Newer Tests for Dry Eye

- Tear Film Osmolarity
- Tear Film Thickness
- **MMP-9**
- MGD Analysis
  - Physical inspection
  - Transillumination
  - Blink Analysis--videography
  - Meibomography
  - MG expressibility (Korb MGE)
- Tear film lipid layer thickness--interferometry

Diagnosis: Other tests

- MMP-9 testing

RPS clinical study
Diagnosis: Other tests

MMP-9 testing—InflammaDry
(CLIA waved)

Dry Eye Disease and MMP-9

Matrix metalloproteinases (MMP) are proteolytic enzymes that are produced by stressed epithelial cells on the ocular surface.

MMP-9 in Tears
- Non-specific inflammatory marker
- Normal range between 3-41 ng/ml
- Correlates with clinical exam findings
- Ocular surface disease (dry eye) demonstrates elevated levels of MMP-9 in tears

All Roads Lead to Elevated MMP-9

- Blepharitis / Meibomian Gland Dysfunction
- Sjogren’s Disease
- Rosacea

Dry Eye / Elevated MMP-9

Diagnosis: Other tests

MMP-9 testing—InflammaDry

- More sensitive marker than clinical signs
  Chotikanovich, Pflugfelder et al IOVS 2009 Jul50(7):3203-9
- Reflects inflammation present before clinical signs
Diagnosis: Other tests

MMP-9 testing—InflammaDry

15 minute in office test

Simple 4-Step Process

Step 1: Collect Sample
Step 2: Assemble Test
Step 3: Run Test
Step 4: Read Results

Diagnosis: Other tests

MMP-9 testing—InflammaDry

237 patient study, 4 trial sites
Tbut, Schirmer, Staining, +/- OSDI
81-86% positive agreement for DES
If MMP-9 negative, 97-98% agreement not dry eye

**InflammaDry Compared to TearLab Osm**

**Osmolality is associated with variability**
- Osmolality levels vary greatly throughout the day
- Reflex tearing may dilute osmolality levels in the tear sample, causing further variability

**MMP-9 is produced by the entire lacrimal system**
- Reliable biomarker for inflammation, consistently elevated in the tears of patients with ocular surface disease
- Reflex tearing does not affect test result

---

**Key Clinical Results**

- **N=237 symptomatic patients**
  - 61% (146/237) confirmed dry eye by TBUT, Schirmer, staining or OSDI
    - Of the 61% confirmed dry eye, InflammaDry was positive 81% of the time
    - Of all symptomatic patients, InflammaDry was positive 53% of the time
  - 39% (80/237) confirmed negative by TBUT, Schirmer, staining and OSDI
    - Of the 39% confirmed negative, InflammaDry was also negative 98% of the time

---

**In patients having symptoms consistent with dry eye disease,**

**InflammaDry is expected to be POSITIVE approximately 50% of the time.**

---

**Cyclosporine and MMP-9**

MMP-9 expression was evaluated by immuno-histochemistry. The mean percentage of MMP-9 expression of the conjunctival epithelial cells was significantly decreased. MMP-9 expression was evaluated semi-quantitatively by measuring cytoplasmic staining for MMP-9.

<table>
<thead>
<tr>
<th>THE EFFECT OF CYCLOSPORINE ON MMP-9 ACTIVITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=24 Eyes of Patients with Thyroid Orbitopathy-related Dry Eye</td>
</tr>
<tr>
<td>MMP-9 Activity Units</td>
</tr>
<tr>
<td>60</td>
</tr>
<tr>
<td>Baseline</td>
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</tbody>
</table>


**Punctal Occlusion**

Punctal occlusion has been shown to improve objective and subjective measures of dry eye to and to exacerbate ocular surface inflammation in subjects with overt clinical inflammation. The Delphi treatment guidelines for ocular surface disorders recommends that inflammatory conditions be treated before punctal occlusion.

Example: Importance of Identifying MMP-9

Dry eye frequently leads to contact lens intolerance

- InflammaDry POSITIVE patients will benefit from the following management plan:
  - Daily disposable contact lens use
  - Cyclosporine
  - Omega 3 fatty acids
  - Punctal occlusion after inflammation controlled

- InflammaDry NEGATIVE symptomatic patients will benefit from the following management plan:
  - Daily disposable contact lens use
  - Omega 3 fatty acids
  - Punctal occlusion

OK, I can only add Osm or MMP-9 for DES

- Which one should I choose?
OK, I can only add Osm or MMP-9 for DED: Which One?

- **Direct comparative study, EARLY DED**
  - 20 patients >60 y.o. to r/o DED
  - T Osm, MMP-9 (incl InflammaDry), Schirmer, TBut, OSDI, Fluorescein staining, LG staining

Results:

- **MMP-9** positive: 1/9 symptomatic and 2/14 suspected mild DED
- **TOsm** positive: 6/9 symptomatic, 9/14 suspected mild DED

Thus: **TOsm** tends to be a more frequent early indicator (n was too small for adeq. P values)

Schargos, et al Cornea 2015 Apr 23

Newer Tests for Dry Eye

- Tear Film Osmolarity
- Tear Film Thickness
- MMP-9
  - **MGD Analysis**
    - Physical inspection
    - Transillumination
    - Blink Analysis--videography
    - Meibomography
    - MG expressibility (Korb MGE)
    - Tear film lipid layer thickness--interferometry
Diagnosis: other tests

Meibomian gland analysis

Why Do This?
Meibomian Gland Dysfunction

- 2011 Report of the International Workshop on meibomian gland dysfunction
- 2 years to complete

The Report of the TFOS Workshop on Meibomian Gland Dysfunction

MGD: Leading Underlying Cause of Dry Eye!¹⁻³

“Meibomian gland dysfunction may well be the leading cause of dry eye disease throughout the world.”
—The International Workshop on Meibomian Gland Dysfunction: Executive Summary

MGD: Underlying Cause of Dry Eye

Ocular Surface Inflammation is often linked to meibomian gland inflammation

“We propose that the ocular surface and the adnexal meibomian glands should be considered as one unit, i.e. the “meibomian gland and ocular surface (MOS) when encountered in the clinical setting”

Suzuki T, Teramakai S, Kinoshita S. Ocul Surf 2015 Apr;13(2)133-149

Prevalence of Evaporative Dry Eye

Recent study by Lemp et al reports 86% of patients evaluated had Evaporative Dry Eye

159 patients

23 Aqueous deficient

14%

79 MGD

50%

57 MGD and aqueous deficient

36%

VDT Dry Eye Severity  
(Computer Vision Syndrome)

Prospective case control study (China)  
106 eyes of 53 patients  
VDT time >4 h/day vs <= 4 h/day  
OSDI, TBUT, Fluorescein staining; Schirmer I  
3 MGD parameters: lid margin abn; meibum score; meibumian gland dropout

Conclusion: MGD is associated with dry eye patients in long term VDT workers with higher OSDI scores—yet may have normal tear volume

Wu, Wang, Dong, Yang, Lin, Shang, Li; PLoS One 2014 Aug 21 e collection

MGD and Daily Soft Contact Lens Use

Study of 41 CL uses vs 31 non-users

- CL wearers statistically worse:
  - Lid margin telangiectasias (OR 6.0)
  - Rounding (OR 9.3)
  - Notching (OR 3.9)
  - Posterior margin hyperemia (OR 4.3)
  - Orifice plugging (OR 4.8)

Greater CL wear duration resulted in greater lid margin abnormalities
MGD is Chronic and Progressive

- Age-standardized prevalence of MGD was 56.3% in study of 3280
- MGD present in 30.5% of adults 40 and over
- 155 of 398 patients (38.9%) exhibited MGD

**References:**

The Pendulum has Swung!
Meibomian Gland Dysfunction

Disease Identification
Standard Patient Evaluation of Eye Dryness (SPEED) Questionnaire (Evaporative Tear Film Deficiency Symptoms)

- Evaluates symptom frequency and severity
- Easy, 2-3 minutes
- Assists to identify symptoms
- Monitor response to treatment

Newer Tests for Dry Eye

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  - Transillumination
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  - Tear film lipid layer thickness--interferometry
Evaluate Meibomian Glands

Meibomian Gland Evaluation

- Normal Glands
Identify Ocular Rosacea

Ocular Rosacea

- Principal cause of MGD
- Chronic inflammatory condition that affects face, nose, forehead, eyes
- Often affects eyes only
- Onset childhood and adults
- More often in fair skinned individuals
- No cure, chronic and progressive if not controlled
Ocular Rosacea

Meibomian Gland Evaluation
Meibomian Gland Evaluation

- Ocular rosacea, selective clogging

Meibomian Gland Evaluation

- Moderate clogging
Meibomian Gland Evaluation

- Early gland drop out

Meibomian Gland Evaluation

- Progressive scarring of orifices
Meibomian Gland Evaluation

- More scarring & glandular drop out

Newer Tests for Dry Eye

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  - **Transillumination**
  - Blink Analysis—videography
  - Meibomography
  - MG expressibility (Korb MGE)
  - Tear film lipid layer thickness—interferometry
Meibomian Gland Evaluation

- Missing gland

Meibomian Gland Tests

Look for gland truncation or dropout
Meibomian Gland Evaluation

- 60% gland loss

Meibomian Gland Evaluation

- Progressive gland drop out (transillumination)
Newer Tests for Dry Eye

- Tear Film Osmolarity
- Tear Film Thickness
- MMP-9
- **MGD Analysis**
  - Physical inspection
  - Transillumination
  - **Blink Analysis**--videography
  - Meibomography
  - MG expressibility (Korb MGE)
  - Tear film lipid layer thickness--interferometry

Diagnosis: Lagophthalmos

- *A common cause of dry eye*
  - Monitor blinking activity at slit lamp
  - Examine for obvious lid scarring
  - Exposure keratitis fluorescein pattern

- Lipiview instrument:
  - measures number of partial blinks!
Blink Analysis

- Lipiview Videography
  - Automated result
  - Can show patients they don’t blink properly

Meibomian Gland Analysis
Complete vs Partial Blinking

Why Measure?
- Partial blinking linked to MGD development
  - 60 patient study with VII nerve palsy for more than 1 week
  - TBUT, fluorescein staining & meibomian gland expression significantly worse w/ incomplete blinkers
  - Subgroup with complete blinking only affected TBUT  Wan T et al Current Eye Research 2015 Apr 2:1-7
Newer Tests for Dry Eye

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Meibomian Gland Tests

Meibomography
Meibomian Gland Tests

Meibomography: non-contact infrared

**OCULUS Keratograph 5M**

More than just a topographer!

The new Keratograph 5M technology is a revolution in corneal topography-sensing light analysis. The high-resolution color camera and the in-sequence map of tear film changes offer a new perspective in the tear film assessment procedure.

Meibography:

- Oculus 5M infrared meibography study
- 128 patients, retrospective
- Meibomian gland atrophy (meiboscore) vs. expressible glands and TBUT and age
- Meiboscores:
  - Worse if poorly expressible p=0.003
  - Worse if lower TBUT p=0.012
  - Worse with age p<.0001
- Lower lid adequate for evaluation
- Lower nasal third often more dropout
- Meibography alone not sufficient for dx of MGD

Meibomian Gland Tests

Meibomography

Sjogrens patients vs non-dry eye controls

- SS group 16% dropout vs. 6.7% (p=0.01)
- SS patients also had reduced LLT (lipid layer thickness) and TBUT

Menzies, Srinivasan, Prokopich, Jones
IOVS 2015 Jan8;56(2):836-41

Meibomian Gland Tests

Meibomography: non-contact infrared + transillumination

Lipiview II (Tear Science)
Newer Tests for Dry Eye

- Tear Film Osmolarity
- Tear Film Thickness
- MMP-9
- **MGD Analysis**
  - Physical inspection
  - Transillumination
  - Blink Analysis–videography
  - Meibomography
- **MG expressibility (Korb MGE)**
  - Tear film lipid layer thickness--interferometry

Meibomian Gland Tests

- Meibomian Gland Evaluator (MGE) (Korb)
  - 0.8-1.2 g/mm2 (moderate pressure)
  - A **physiologic test** like Schirmer & Osm

<6 secreting glands: should Rx
Newer Tests for Dry Eye

- Tear Film Osmolarity
- Tear Film Thickness
- MMP-9
- MGD Analysis
  - Physical inspection
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  - MG expressibility (Korb MGE)
- Tear film lipid layer thickness—interferometry

Meibomian gland analysis

Tear Film Lipid Layer thickness
LipiView® Ocular Surface Interferometer
Measures Lipid Layer in Nanometers

Device dimensions: 28” x 17” x 17”
Measurement time: 20 seconds per eye

Light source: The Illuminator
Chin rest
Camera, computer and drivers are housed by the device

Finis, Geerling et al., Evaluation of Lipid Layer Thickness Measurement of the Tear Film as a Diagnostic Tool for Meibomian Gland Dysfunction, Cornea 2013, Oct 3 E-pub ahead of print
LipiView® Report

Results are displayed for printout & patient education

- Evaluate the lipid layer and blink profile
- Educate patients
- Monitor treatment response
- Predict treatment outcome based on identification of partial blink (PB)

Diagnosis: Lagophthalmos

- A common cause of dry eye
  - Monitor blinking activity at slit lamp
  - Examine for obvious lid scarring
  - Exposure keratitis fluorescein pattern

- Lipiview instrument:
  - measures number of partial blinks!
So, how do I diagnose dry eye?

- Pre examination Intake Questionnaire (SPEED index), Medical History, Ophthalmic history (CL wear, LVC, cataract surgery, other risk factors)
- Interview: Let the patient tell their story

If symptoms warrant, examine the patient with high degree of suspicion

So, how do I diagnose dry eye?

- Severe cases: easy clinical diagnosis by signs +/- tear test
  - *caution: most severe cases often asymptomatic

- Mild cases: establishing diagnosis is difficult (Osm or other tests may help):
  - symptoms most important feature
So, how do I diagnose dry eye?

Patients should have one ocular symptom and one ocular sign:

**Symptoms**:
- Daily, persistent, troublesome dry eyes for more than 3 months;
- Recurrent sensation of sand or gravel in eyes or:
- Use of tear substitutes more than 3x/day

**Signs**:
- Look for MGD (<6 functioning glands per lower lid) (use MGE—Tear Science); entropic orifices, inspissation, telangiectatic vessels
- Typical **fluorescein** staining pattern (@ 2 minutes)
- Positive **lissamine green** or **rose bengal** staining, or
- Positive result on **Schirmer** test, consider **Osm**
So, how do I diagnose dry eye?

Patients should have one ocular symptom and one ocular sign:

- **Signs**
  - If MGD suspected, I schedule patient for Lipiview evaluation
  - Comprises
    - meibum thickness
    - Incomplete blinking analysis
    - MGE: # functioning glands lower lids
    - Meiboscopy (muscle light, soon Lipiview II meibography)

- Once dry eye diagnosed, attempt to determine severity
  - Useful for explaining prognosis to the patient
  - Explain patient has a disease,
  - Explain risk of not treating disease
My Treatment Paradigm — In a nutshell

- Treat the MGD first (3-4 months)
- MGD treatments generally assist aqueous component, reduces ongoing “fuel to the fire” inflammation (MOS)
- Finish with augmentation of aqueous component if necessary
- Mucus issues generally improve but may require additional interventions
TREATMENT

Dry Eye Treatment

DES

Peter Cushing making a difference
Dry Eye Severity Classification & Treatment Overview

- DEWS Workshop proposed 4 Dry Eye severity levels
- Emphasized early and aggressive treatment appears to
  - improve quality of life
  - Prevent potentially blinding complications

DEWS Workshop Report 2007; Ocular Surface Apr;5(2)

Dry Eye Severity Classification & Treatment Overview

- Adopt strategies that
  - Stimulate natural tear constituents
  - Maintain surface epithelial health/barrier function
  - Inhibit inflammatory factors that adversely impact ability of ocular surface and glandular epithelia to produce tears

DEWS Workshop Report 2007; Ocular Surface Apr;5(2)
Dry Eye Severity Classification & Treatment Overview

Severity level 1
Mildest signs and symptoms

- Discomfort: mild and/or episodic occurs under environmental stress
- Visual symptoms: none or episodic
- Conjunctival signs: none to mild
- Corneal/tear signs: none to mild
- Lid/meibomian glands: mgd variable (NOMGD)
- Schirmer: variable

DEWS Workshop Report 2007; Ocular Surface Apr;5(2)

Dry Eye Severity Classification & Treatment Overview

Severity level 1 (Mildest signs and symptoms)

Treatment:

- Limit dessicating medications (antihistamines, decongestants)
- Environmental strategies (avoid low humidity and air conditioning drafts)
- Lid hygiene/meibomian gland function treatments e.g. Lipiflow (most wait until level 2!)
- OTC lubricants

DEWS Workshop Report 2007; Ocular Surface Apr;5(2)
Dry Eye Severity Classification & Treatment Overview

Severity level 1

Treatment (cont):

OTC lubricants

- Do not use preserved tears more than 4-6x/day, especially BAK…

Human corneal epithelial cells toxicity comparisons

A. DEAD CONTROL
B. LIVE CONTROL
C. GENTAMICIN
D. LATANOPROST
E. HP-GUAR GELLABLE LUBRICANT EYEDROP SOLUTION
F. TRAVOPROST WITHOUT BAK

Paisley, Yee 2007
Dry Eye Severity Classification & Treatment Overview

Severity level 1 Treatment (cont):
OTC lubricants
- Do not use preserved tears more than 4-6x/day, especially BAK
- Alternative preservatives
  - Chlorbutanol
  - Polyquad
  - EDTA
  - PHMB

Severity level 1 Treatment (cont):
OTC lubricants
- Alternative preservatives (cont)
  - Purite (stabilized oxychloro complex), an oxidizing preservative
    - Light exposure: sodium & chlorine free radicals, water and oxygen
      - (e.g. Refresh Tears, Alphagan P)
  - Gen Aqua (sodium perborate)
    - Catalyzed into H2O2, water, oxygen
      - (Genteal)
Dry Eye Severity Classification & Treatment Overview

Severity level 1 Treatment (cont):

- OTC lubricants
- Alternative preservatives (cont)
  - SofZia, an oxidizing preservative
    Exposure to the eye (cations) inactivates the preservative
    (Travatan Z, not yet in tears)

Severity level 2

- Discomfort/severity & frequency: moderate episodic, with or without environmental stress
- Visual symptoms: annoying and/or activity limiting, episodic
- Conjunctival signs: none to mild
- Corneal staining: variable
- MGD variably present (More often than not!!!)
- Schirmer ≤ 10 mm
Dry Eye Severity Classification & Treatment Overview

Severity level 2 Treatment:
Severity level 1 treatments prove inadequate

- Address the inflammatory component
  - Topical steroids
  - Cyclosporine
- Treat MGD, rosacea (lid hygiene, Lipiflow)
- Punctal plugs AFTER mgd & inflammation controlled
- Moisture chamber spectacles
- Lacriserts select cases

DRUGS/ Interventions (cont):
- Tetracyclines (for meibomitis, rosacea), vs omega 3 fatty acids
- Topical steroids—Loteprednol 0.5% gel, oint. (Lotemax)
  - Fluorometholone 0.1% (FML)
- Topical cyclosporine—Restasis; tacrolimus (FK-506)
- Secretagogues
- Punctal plugs (after inflammation controlled)
Dry Eye Severity Classification & Treatment Overview

Severity level 2 Treatment (cont):

DRUGS/ Interventions

No secretogogue FDA approved for dry eyes

- Oral
  - Pilocarpine (Salagen)

- Topical
  - Diquafosol (Prolacria-Phase III) (surface cell production of mucin, fluid, ± lipid from MG)
  - Eicosanoid 15-(S)-HETE (MUC1 mucus)
  - Ecabet sodium (goblet/ epithelial cell mucus)
  - Rebamipide (mucin)

- Punctal plugs (after inflammation controlled)
  - Beneficial outcomes reported in 74-86% of patients treated in various studies
  - Postulated feedback mechanism to regulate tear production by lacrimal gland, i.e. significant decrease in tear production for up to 2 weeks after plug insertion
Dry Eye Severity Classification & Treatment Overview

Severity level 3
- Discomfort frequently severe, or constant without environmental stress
- Visual symptoms annoying, chronic &/or constant limiting activity
- Conjunctiva: +/- injection; moderate to marked staining
- Cornea: increased tear debris, mucus clumping, filaments
- MGD/ lid problems frequent
- Schirmer ≤ 5 mm

Severity level 3 Treatment (cont):
If level 1 & 2 treatments fail:
- Never use preserved or “disappearing preservative” tears, gels or ointments
- Preservative free tears:
  - Unit dose
  - Spray (mist, liposomes)
  - Multidose silver tip (Visine Tears)
  - VIVA drops with vitamin A (Avitears)
- ASED’s
Dry Eye Severity Classification & Treatment Overview

Severity level 3 Treatment (cont):
If level 1 & 2 treatments fail:
- Autologous serum eye drops (20-100%)
- Permanent punctal occlusion
- Therapeutic contact lenses
  - PROSE, Scleral vaulting contact lenses

Severity level 4:
- Severe &/or disabling, constant discomfort
- Visual symptoms constant or disabling
- Conjunctiva: injected, marked staining
- Cornea: severe punctate erosions
- Increased tear debris, mucus clumping, filaments, ulceration
- Lids: keratinization, trichiasis, symblepharon
- Schirmer I: ≤ 2 mm
Dry Eye Severity Classification & Treatment Overview

**Severity level 4 Treatment:**
If level 3 treatments are inadequate:

- Systemic antiinflammatory agents (e.g. Sjogrens tx's)
- Surgery
  - Lid surgery: Tarsorrhaphy, ectropion and scleral show repairs
- Grafting: amniotic membrane, buccal mucus membrane, salivary gland transplantation

**Summary**

- “What is dry eye?”
- Etiologic classification
  - Aqueous deficient
  - Evaporative
  - “Environmental” contributions
    - Intrinsic/systemic
    - Extrinsic
  - Delicate balance of healthy tears
    - Mucus, aqueous & lipid
Summary

- Diagnostic tools
  - Questionnaires
  - Testing
- 4 levels of Dry Eye Severity (DEWS)
- Overview of Treatment Strategies

Next Up

- Current & Future Treatment Options for Dry Eye
Dry Eye: Etiology & Diagnosis

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