Dry Eye Disease

- 42% of patients complain of symptoms that would indicate DED (60-80M people)
- 30-50 Million in the North America based on longitudinal studies
- 16 Million diagnosed with DED
- About 42% of all eye exams have a primary or secondary complaint that would indicate DED

Lacrical Functional Unit (LFU)

- Tear film
- Lacrical glands
- Corneal and conjunctival epithelia
- Meibomian glands
- Homeostasis controlled by nerve connections and systemic hormones

Begin with the Lid in Mind

Frothy / Foamy Tears = MGD
Significant Signs of Blepharitis

Collarettes/volcano sign

Telangiectatic vessels

Capped MG’s
5 Triaging Questions from OD Summit

1. Do your eyes ever feel irritated, dry or burn?
2. Are your eyes red?
3. Do you experience blurred vision especially fluctuating vision?
4. Do you use or have the urge to use artificial tears?
5. How much time do you spend on digital devices per day?
Risk Factors for Dry Eye Disease

- Systemic Medications
- Topical Medications
- Age
- Gender
- Contact Lens Wear
- Ocular Surgery
- Environment
- Digital Devices
- Systemic Disease
- Smoking
- Certain Anterior Segment Diseases

Questionnaires

DEQ-5
OSDI
SPEED

This page contains information about risk factors for dry eye disease and questionnaires used to assess dry eye symptoms. It includes diagrams illustrating diagnostic tests and symptoms associated with dry eye disorder.
Identify the Sub-type of DED
Diagnostic Summary

1. Symptoms (most significant and when)
2. Global test for homeostasis
   - Osmolarity
   - Ocular surface staining
3. Subtype
   - MG Expression
   - Meniscus height
KB Light Test

OBSTRUCTION
- Blink exercises
- Moist heat compress
- Lid debridement
- Thermal expression
- LLLT/IPL
- Lid seals

BIOFILM
- Blepharostasis
- Hypochlorous acid
- Manuka vs. Tea Tree
- Surfactant cleansers
- LLLT/IPL

INFLAMMATION
- Lifitegrast
- Cyclosporine
- Corticosteroids
- Omega fatty acids
- PO Doxycycline
- PO Azithromycin
- Topical macrolides
- IPL

TEAR FILM
- Artificial tears
- Environment changes
- Increase hydration
- Neurostimulation
- Brimonidine 0.25%

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Bacterial Biofilm in Lash Follicles

OBSTRUCTION BIOFILM INFLAMMATION TEAR FILM

- Blink exercises
- Moist heat compress
- Lid debridement
- Thermal expression
- LLLT/IPL
- Lid seals
- Blepharoexfoliation
- N-Chlorotaurine (NCT)
- Hypochlorous acid
- Manuka vs. Tea Tree
- Surfactant cleaners
- LLLT/IPL
- PO Doxycycline
- PO Azithromycin
- Topical macrolides
- IPL
- Artificial tears
- Environment changes
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- Brimonidine 0.25%

White Blood Cell in Action

- Hypochlorous acid (HOCI)
- N-Chlorotaurine (NCT)
- Natural Compound
- Rapid Acting
- Stable Formulation
- BUT Unstable

White Blood Cell in Action

- Red Blood Cells
- Hypochlorous acid

White Blood Cell in Action

- N-Chlorotaurine (NCT)
- Natural Compound
- Rapid Acting
- Stable Formulation
- BUT Unstable

Daily Eyelid Cleaning Brush

- Two pronounced pads express meibomian glands on upper and lower eyelids
- Tapered bristles allow micro-blepharo exfoliation on both eyelid margins at the same time
- Outer bristles target the crevices between the upper and lower lashes, while the center bristles target the upper and lower eyelid margin
- Contoured brush pattern matches the eyelid margin from the medial canthus to the lateral canthus
- Medical canthus scrub
- Lateral canthus scrub
- One pump of Manuka/Coconut/Aloe Hydrating Lids and Lash Cleansing Gel per eye
- Simple to use, up and down, and circular motion for gentle scrubbing of eyelids
- Easy grip using index, middle finger, and thumb

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Randomized Single Blind Controlled Clinical Trial

- Study conducted by the University of Notre Dame (Department of Biological Sciences) with Michiana Eye Center, the University of Colorado, the Kentucky Eye Institute, and Danelli Ocular Creations LLC (Evaluation of SUMMIT BRUSH in Treatment of Blepharitis).
- IRB (19-12-5734) and ClinicalTrials.gov (NCT04603222).
- Slit Lamp Biomicroscopy and counts of collarettes, clear sleeves, and scurfs associated with blepharitis on the eyelid margins.
- BRUSH with Lid Scrub Original Foaming Eyelid Cleanser compared to foaming eyelid cleanser alone.

Treatment Brush and Control foam reduce the number of eyelid features

Preliminary analysis of eyelid treatment mean +/- standard error of the mean

Two factor repeated measures ANOVA: significant reduction in the number of eyelid features at 2 weeks and 1 month (p < 0.05).

Effectiveness of Treatment Brush vs. Control Foam

- 91% of subjects treated with treatment brush reduced features by ≥ 50% by 4 weeks.
- By comparison, only 38% of control foam subjects reached a ≥ 50% reduction by 4 weeks.
- 55% subjects treated with treatment brush reduced features by ≥ 87% by 4 weeks.
- By comparison, only 1 control foam subject reached a high level of reduction, this being 87%.
- Best response to treatment brush was a 94% reduction in features, occurring in 2 subjects at 4 weeks.

CONCLUSION: Treatment Brush is more effective at reducing the numbers of collarettes, clear sleeves, and scurfs on the eyelid margins, key features of blepharitis and Demodex.

Treatment Brush reduces Speed Score by an additional 28% over Control foam when measured at 2 weeks

Preliminary analysis of Speed Score: Percentage decrease compared to before treatment

1-test at 2 weeks of treatment (* p < 0.05) reveals significant difference between treatment groups in percentage decrease in number of eyelid features.
IPL and LLLT

- Telangiectatic vessels and skin erythema release inflammatory mediators
- IPL targets the abnormal erythematous blood vessels
- Affects mitochondrial activity
- Temperature effect on glands?
- Photomodulation affecting cytochrome C or activating fibroblasts and collagen synthesis
Omega fatty acids and Dry Eye

- LA / GLA (ω-6)
  - Increase "good" PG (PGE-1)
  - Against ocular surface inflammation
  - Increase tear production
- Help to maintain MG function (Macsai, 2008)

Supplemental GLA for Dry Eye: 7 Controlled Clinical Trials

- Contact lens (Kokke KH et al. Contact Lens Ant. Eye 31:141-6, 2008.)
- Post-menopausal women (HydroEye) (Sheppard JD, Pfugfelder SC, et al. Cornea 32:1297-1304, 2013.)

Effectiveness & Safety

- Current OTC vasoconstrictors are α1- or α1/α2-adrenergic receptor (α-AR) agonists1,2
  - Selective α1-AR agonists (phenylephrine, tetrahydrozoline)
  - Mixed α1/α2-AR agonists (naphazoline, oxymetazoline)
- Long-term use restricted by:3-6
  - Tachyphylaxis (tolerance or loss of effectiveness)
  - Redness rebound upon discontinuation (worsening vs. baseline)
  - Pupil dilation
  - Systemic side effects (e.g. somnolence, dizziness)
  - α1-ARs predominantly expressed in arteries (vs. α2-ARs in veins)7,8
  - Internalization/downregulation of α1-ARs (tachyphylaxis)
  - Vasoconstrictor-induced tissue ischemia and vasodilator release (rebound redness)

Mechanism of Action

- $\alpha-1$ or mixed $\alpha-1/\alpha-2$ Effect
  Generalized Arteriolar/ Venular Constriction Creates Ischemia

- Selective $\alpha-2$ Effect
  Preferential Venular Constriction
  Reduced Ischemia

Clinical Study Efficacy

- Eyes before treatment (baseline)
  Brimonidine 0.025% OD
  Oxymetazoline OS
  (5 minutes post-dose)

Phase 3 Efficacy (BL861) – Patient Diary Assessments

- Sustained efficacy across treatment period without tachyphylaxis
- No evidence of rebound after cessation of treatment

Mean redness scores drawn from patient diary assessments

Aqueous Deficient Dry Eye Disease Management

- Lifitegrast
- Cyclosporine
- Corticosteroids (Loteprednol)
- Omega fatty acids
- PO Doxycycline
- Amniotic membrane
- Cytokine extract

Monitor for MGD

INFLAMMATION
- Artificial tears
- Environment changes
- Increase hydration
- Punctal occlusion
- Neurostimulation
- Cevimeline PO (Evoxac)
- Autologous serum q2h
- Scleral lenses

TEAR VOLUME

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Dry eye is a chronic inflammatory disease with flares that are characterized by acute exacerbations of signs and/or symptoms.

- Loteprednol 0.25% approved for short term signs and symptoms of DED (QID for up to 2 weeks)
- Most dry eye disease patients with or without maintenance dry eye therapy, experience flares and desire rapid relief.
- Regardless of dry eye severity, flares typically occur 4-6 times per year

Loteprednol 0.25% Mucus Penetrating Particles (MPP) Drug Delivery Technology

Traditional Suspension Eye Drop

Loteprednol 0.25% Mucus-Penetrating Particles Drug Delivery Technology

180 Day Extended Duration Punctal Plugs

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TAKEAWAYS FROM TRIALS

- Array of positive endpoints reflects broad mechanism of action of neuromodulation
- Effective for aqueous tear deficiency and meibomian gland disease
- Acute, sub acute, and chronic benefits to the ocular surface
- Outstanding safety profile
- High value product for dry eye

ACTIVATES CENTRAL REFLEX WHICH RESULTS IN ACTIVATION OF LACRIMAL FUNCTIONAL UNIT

External Nasal Nerve

A NOVEL NEUROSTIMULATION APPROACH WITH SONIC ENERGY

- Drug free, home use, fast onset of action with sustained effect
- Handheld, battery powered device with no disposable component
- Externally applied
- Doctor prescribed, 15s Training

** Investigational Device, Not FDA Cleared

Monitor for MGD

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What is Amnion?

- Innermost layer of the fetal membrane & placenta
- Contains anti-inflammatory cytokinesis and growth factors
- Harvested in a sterile environment from placental tissue obtained during elective cesarean sections from healthy mothers
- Donors are screened for transmissible disease

Benefits of Amnion

- Promotes Epithelialization
- Suppresses inflammation
- Inhibits scarring
- Inhibits angiogenesis
- Anti-microbial agent
- Disadvantages: Short term benefit

Amniotic Membrane Types

- **Cryopreserved**
  - Pros
    - FDA Approved
    - Proprietary Freezing Process
    - Ease of use (fitting a contact lens)
  - Cons
    - Requires refrigeration and space in office
    - Has to be thawed before use
    - Ring placement can be uncomfortable
    - Shorter shelf-life
    - Price

- **Dehydrated**
  - Pros
    - Patient comfort
    - Variety of sizes
    - Reduced cost
    - Ease of use
    - Requires BCL for retention or Lid Seal
  - Cons
    - BCL can cause hypoxia
    - Amniotic Membrane
  - Sizes: 8mm, 10mm, 12mm & 14mm
  - Stored at room temperature
  - Shelf life of 5 years
  - Product can be placed either side down on ocular surface

**Action of Growth Factors in Serum**

- Cellular proliferation
- Migration
- Differentiation
- Apoptosis
- Intercellular communication

**Autologous Serum Tear Substitutes**

First described 1994 by Fox et al (for KCS), more after success in eyes with persistent epithelial defects (Tsubota et al 1999)

<table>
<thead>
<tr>
<th>Protein</th>
<th>Abbreviation</th>
</tr>
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<tbody>
<tr>
<td>Growth differentiation factor 5</td>
<td>GDF-5</td>
</tr>
<tr>
<td>Interleukin 5a</td>
<td>IL-5a</td>
</tr>
<tr>
<td>Interleukin 1 Delta</td>
<td>IL-1D</td>
</tr>
<tr>
<td>Interleukin 1 receptor antagonist</td>
<td>IL-1ra</td>
</tr>
<tr>
<td>Interleukin 12 p40</td>
<td>IL-12p40</td>
</tr>
<tr>
<td>Interleukin 17</td>
<td>IL-17</td>
</tr>
<tr>
<td>Osteoprotegerin</td>
<td>OPG</td>
</tr>
<tr>
<td>Interleukin 8</td>
<td>IL-8</td>
</tr>
<tr>
<td>Interleukin adhesion molecule 1</td>
<td>ICAM-1</td>
</tr>
<tr>
<td>Tumor necrosis factor</td>
<td>TNF</td>
</tr>
<tr>
<td>Interleukin 4 receptor</td>
<td>IL-4R</td>
</tr>
<tr>
<td>Macrophage colony-stimulating factor 1 receptor</td>
<td>M-CSFR</td>
</tr>
<tr>
<td>B lymphocyte chemotaxinactant</td>
<td>(CKX, 135)</td>
</tr>
<tr>
<td>Estesin 2</td>
<td>Estesin-2</td>
</tr>
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**Ocular Surface Disorders**

**Diseases with Pre-existing Epithelial Defects**
- Neovascular pannus
- Corneal epithelial defect
- Post-refractive neovascularisation
- Herpetic, viral, and fungal keratitis

**Diseases without Epithelial Defects**
- Dry eye syndrome
- Superficial punctate keratopathy
- Inflammatory keratitis
- Radiation keratitis
- Wound dehiscence
- Exposure (Surgisis keratopathy)

**Diseases with Unhealthy Epithelium or Irritated Membrane**
- Recurrent corneal erosion, BRB
- Saloxen's meibomian depletion
- Scleral keratopathy
- Trauma after PK
- Pterygium, bullous keratopathy
- Corneal dystrophy (e.g., Fuchs Dystrophy)

**Monitor for MGD**

- Lifitegrast
- Cyclosporine
- Corticosteroids (Loteprednol)
- Omega fatty acids
- PO Doxycycline
- Amniotic membrane
- Cytokine extract

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National Outfit for ASED

- Present in almost every major city in the US
- Blood draw at patients home or work
- Processing
- Regular replacement
- Doctors must specify concentration
  - 20% for most patients
  - 40% for GVHD etc.

KOL Serum Tears Survey

Overview

Six Respondents

- Victoria Chin, OD, Mann Eye Institute
- Paul Karpecki, OD, Kentucky Eye Institute
- Marjan Farid, MD, University of California, Irvine
- Pedram Hamrah, MD, New England Eye Center – Tufts
- Shachar Tauber, MD, Mercy Clinic Eye Specialists
- Winston Chamberlain, MD, Casey Eye Institute

Key Questions

- How do you decide on starting therapy with serum tears in a dry eye patient with unspecified symptoms or significant MGD?
- What is your preferred starting formulation of serum tears?
- Are there particular types of patients you have found respond well to serum tears?
- What percentage of moderate and severe patients do you prescribe serum tears?

KOL Serum Tears Survey Results

Prior Treatment History

- Non-insured or high deductible
- Rheumatologic Disease
- Desires homeopathic
- Exhausted all options

Yes, I skip straight to serum when there is significant surface punctate keratitis.

Skip straight to serum tears for Neuroptic patients, particularly post-surgical patients.

Most common reason to do serum when failed OTC or insurance covered dry eye treatments, including above mentioned therapies minus AMT which I rarely use for dry eye.

Yes, if I diagnose SS KCS, I move directly to ordering ASEDs in some patients. Otherwise I typically begin with topical steroids and if there is no significant improvement after 1 month, go to biologics.

Take Aways

Use serum tears in uncontrolled patients despite OTC, plugs, or Rx. Some said skip straight to serum for neuropathic patients, significant punctate keratitis.

KOL Serum Tears Survey Results

What is the preferred starting formulation?

40% 4 Times/Day

75% 8 Times/Day

20% 8 Times/Day

40% 6 Times/Day

50% 6 Times/Day

20% 6 Times/Day

Take Aways

Survey Answers Varied

Rx Data Average Shows:

>60% Providers in 2020

Began with 20% 4-8 Drops/Day

KOL Serum Tears Survey Results

What percent of moderate and severe DED patients do you put on serum tears?

10% Moderate

50% Severe

20-30% Moderate

20% Moderate

70-80% Severe

100% Severe

10-15% Moderate

90%+ Severe

Take Aways

Average: 15-30% in Moderates and 60-100% in Severe

KOL Serum Tears Survey Results

Who responds the best to serum tears?

- Inflammatory etiology (rheumatologic, BJS, Gout, Rosacea, severe allergies)
- Most patients with DED respond well
- Patients with surface disease do well as long as not severe stage 1 NK
- Neuroptic patients that do respond to anesthetic drops
- Autoimmune, Herpetic, Neuroptic Pts.

Take Aways

YES for neuropathic pain patients, maybe for neurotrophic keratitis

More severe disease, including GVHD and Sjogren's

Averages: 15-30% in Moderates and 60-100% in Severe
Mucin Deficient DED

- Stage 1: Conjunctival staining
- Stage 2: Mucin strands
- Stage 3: Filamentary keratitis

Monitor for MGD

SCLERAL LENSES

- Lifitegrast
- Cyclosporine
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SCLERAL LENSES

Mucin Deficient DED

- Stage 1: Conjunctival staining
- Stage 2: Mucin strands
- Stage 3: Filamentary keratitis
MUCIN QUALITY
INFLAMMATION/MUC EXPRESSION
• Topical corticosteroids (fluoromethalone)
• Cyclosporine
• Lifitegrast
• Autologous Serum
• Cytokine extract drops

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MUCIN QUALITY
INFLAMMATION/MUC EXPRESSION
• Artificial Tears (HA based)
• Vitamin A ung
• Punctal occlusion
• Brimonidine 0.025%
• Acetylcysteine 10%

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Active Ingredients
- White Petrolatum (90%), Lanolin (6.9%), Light Mineral Oil (1.4%)
- Retinol Palmitate (Vitamin A)
- Yes
- Yes
- 6 months
- 0.18 fl. oz. (5g)
- 300
- Moderate to Severe Forms of Dry Eye which require a more viscous ointment. Recommended for night time use

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OSD CONCLUSIONS

- Start with the LID in mind
- Follow a straight forward diagnostic algorithm
- Treatment: O B I T vs. I TV
- Incorporate new and effective technologies
- Communicate effectively
- Make a difference in your patient's lives

Thank You

karpecki@karpecki.com

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