Dry Eye Disease: Advancements in Therapy

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What We Will Cover…

- Dry eye definition and background information
- Associated conditions and risk factors
- Brief overview of dry eye pathophysiology
- Brief review of diagnostic equipment
- Review of available treatment options
- Mechanism of action of available treatments
- Treatments on the forefront

I do not have any financial relationships to disclose.

Dry Eye Defined…

- Definition by the Tear Film & Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II) 2017

- Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles.

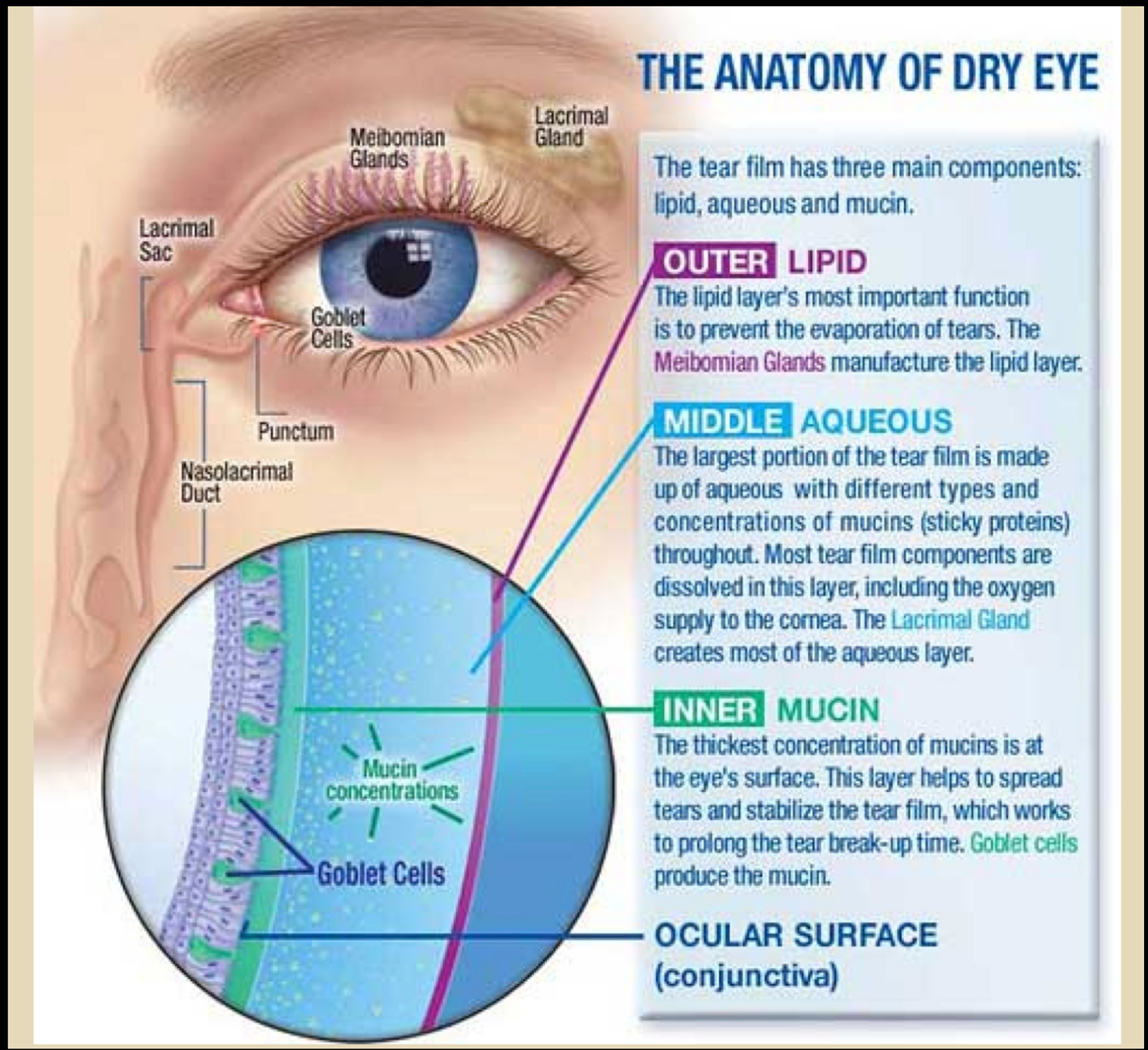
- Vision starts with the tear film as the 1st refractive surface so DED is a vision impacting disease!!!

Dry Eye

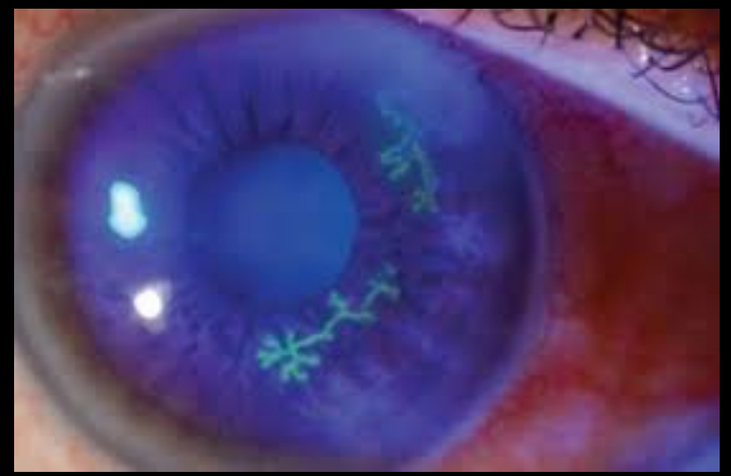
- Approximately 20 million people in the U.S. (344 million people worldwide) have dry eye disease (DED)
- A.K.A.: Dry eye syndrome, dysfunctional tear syndrome
- Difficult disease to treatment and monitor due to:
  - Lack of correlation between signs and symptoms
  - Overlapping conditions and subtypes
  - Poorly understood pathophysiology of the disease

Subtypes of Dry Eye

- Evaporative (most common)
- Aqueous deficiency
- Mucin deficiency
- Exposure related
- Neuropathic pain
- These can overlap!!!
- Common cycle of inflammation in all subtypes



Contributors and Risk Factors



- Aging
- Female gender
- Decrease in supportive factors (hormones)
- BAK (benazlkonium chloride) containing topical medications (glaucoma meds)
- Ocular surface conditions affecting the trigeminal afferent sensory nerves (HSV keratitis, LASIK surgery)

- Radiation
- Environmental and extrinsic factors: reduced humidity, increased wind, air conditioning/heating, allergens, smoking, contact lens wear, screen time

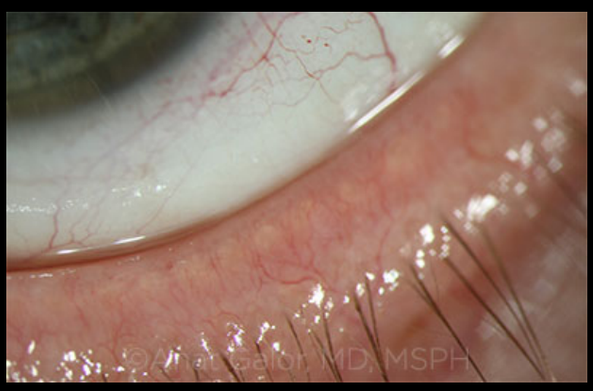
Contributors and Risk Factors: Medications

- Systemic medications that disrupt efferent cholinergic nerves that stimulate tear secretion
    - antihistamines, antidepressants, antipsychotics, anxiolytics, and anticholinergics decrease LG output
- Antihypertensives (HCTZ, beta blockers) decrease intravascular volume and limit LG output
- Hormone manipulators (especially decrease in testosterone) impact meibum production
- Botulinum toxin can lead to decrease in blink force and limited tear spread and meibum delivery

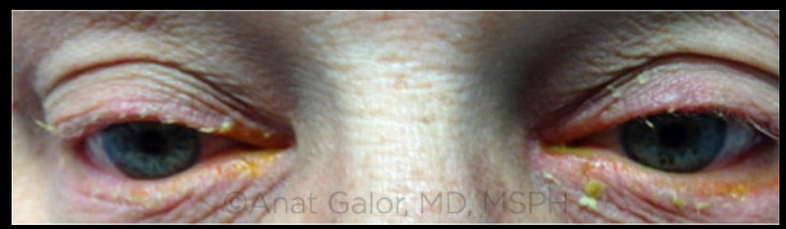
Contributors and Risk Factors: Eyelid Conditions

- Parkinson Disease: infrequent blinking
- Lid Laxity/Floppy eyelid syndrome may lead to incomplete lid closure
- Thyroid disease: lid retraction and lagopthalmos can lead to exposure

- Bells Palsy: lagophthalmos and exposure
- Eyelid mass/lesions, eyelid and/or conjunctival laxity or conjunctival lesions can all affect ocular surface stability



- Rosacea can be associated with Meibomian gland dysfunction
- Blepharitis is chronic and inflammation can lead to poor tear quality
- Lid malposition: ectropion/entropion can lead to incomplete lid closure and exposure

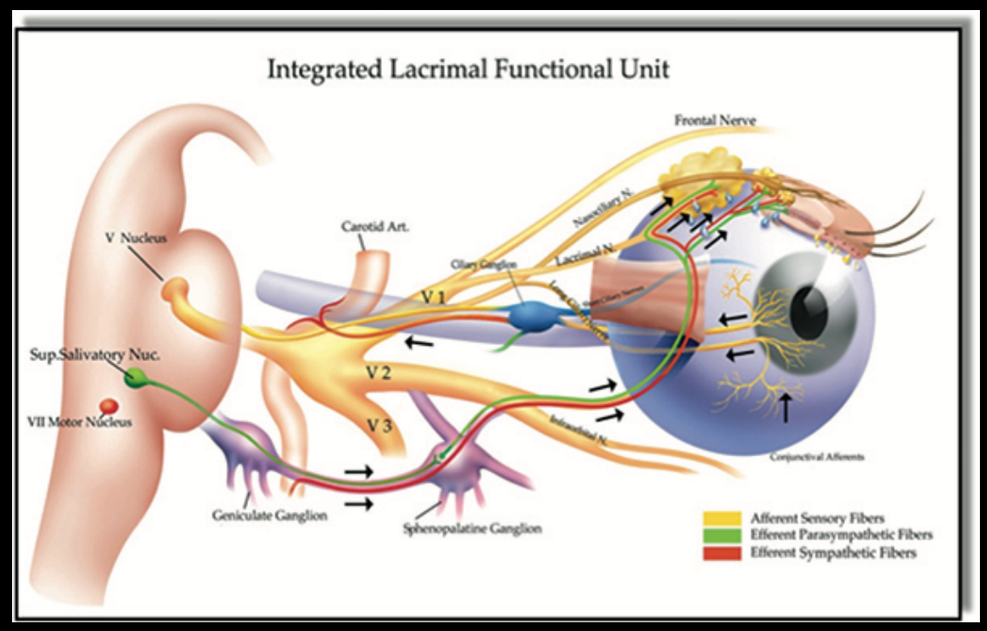


Contributors and Risk Factors: Systemic Conditions

- Systemic inflammatory conditions: (Sjögren syndrome, rheumatoid arthritis, lupus)
    - Sjögren syndrome: inflammatory cellular infiltration of exocrine glands (lacrimal)
        - About 10% of patients with aqueous deficient dry eye have underlying Sjögren syndrome and clinicians should keep this in mind and test when suspicious (these patients have increased risk of malignancy)
- Lacrimal gland infiltrative conditions: lymphoma, sarcoidosis, hemochromatosis, amyloidosis, viral infections (including HIV, HCV)
- Graft-versus-host disease (infiltration of lacrimal glands and co
- Ocular mucous membrane pemphigoid and Stevens-Johnson (inflammation, scarring, goblet cell destruction)

Pathophysiology

- Multifactorial condition resulting in a dysfunctional lacrimal functional unit leading to a vicious cycle of inflammation on the ocular surface
- Dysfunction/disease of tear secretory glands—> changes in tear composition—> hyperosmolarity—> stimulates productions of inflammatory mediators (tear fluid, conjunctiva and lacrimal glands) —> may lead to dysfunction/disappearance of cells responsible for tear secretion … and the cycle continues
- The previously mentioned contributors/risk factors may initiate or add to the inflammatory process



Inflammation in Dry Eye

- Increased inflammatory mediators in the tear fluid, conjuctiva and lacrimal glands:
    - cytokines, chemokines, metalloproteinases and increase in T cells in the conjunctiva
- Tear film hyperosmolarity is common in all types of DED and is a pro-inflammatory stimulus
- We can try to target specific inflammatory markers for diagnosis and treatment

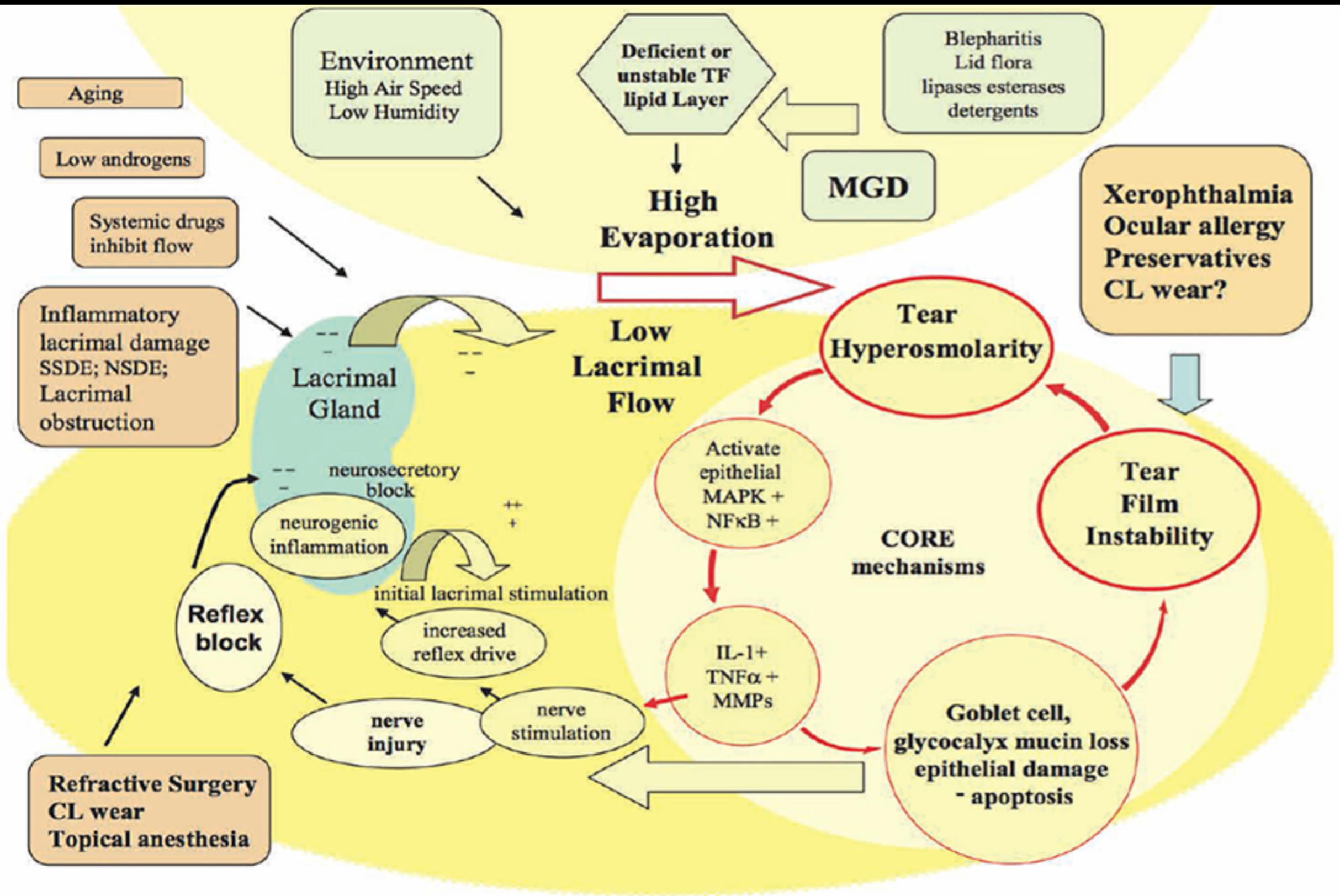
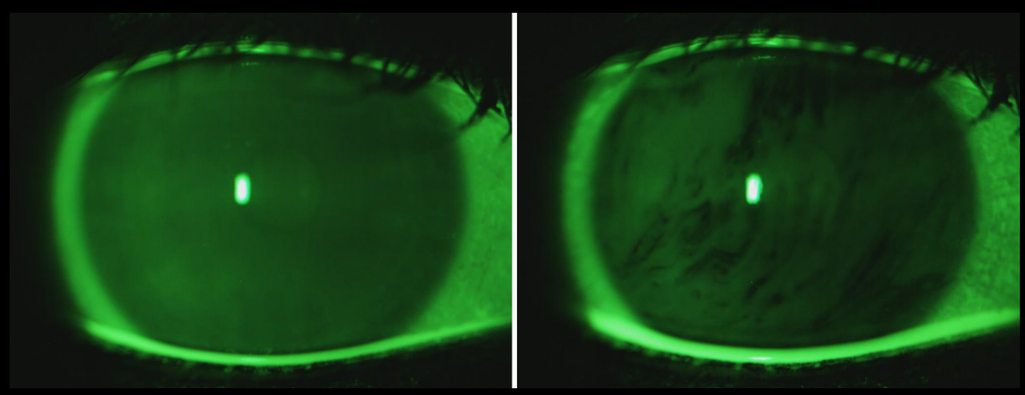
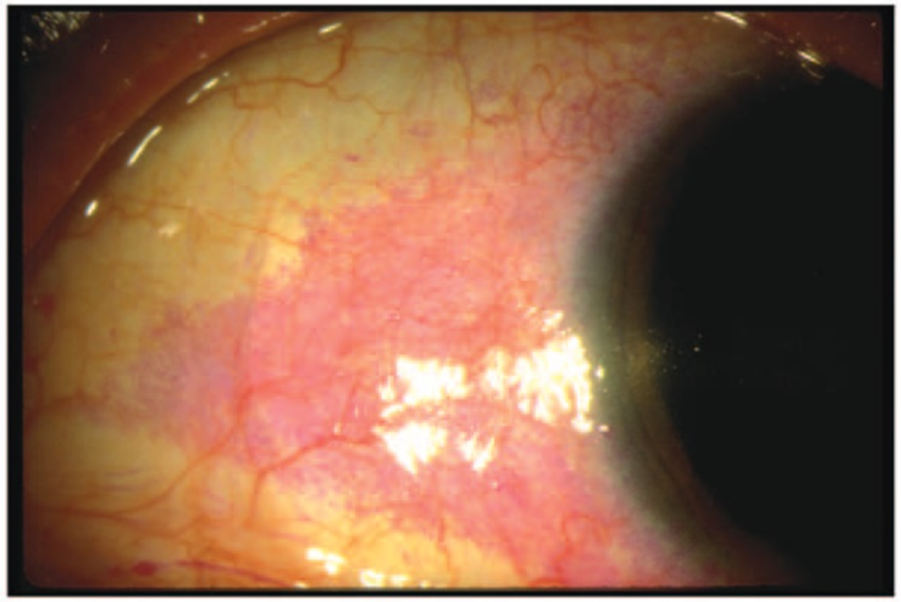


Figure 1. Inflammation drives and results from aqueous-deficient dry eye and evaporative dry eye in a chronic downward cycle.[1]

Diagnostics

- Ocular surface staining: wait 90-120 sec after instillation for best results
    - Staining with fluorescein (usually inferior cornea)
    - Lissamine green or rose bengal staining of the conjunctiva
- TBUT (<10sec)
- Tear meniscus (<10mm after 5 min)
- Schirmer test
- MG expression and appearance



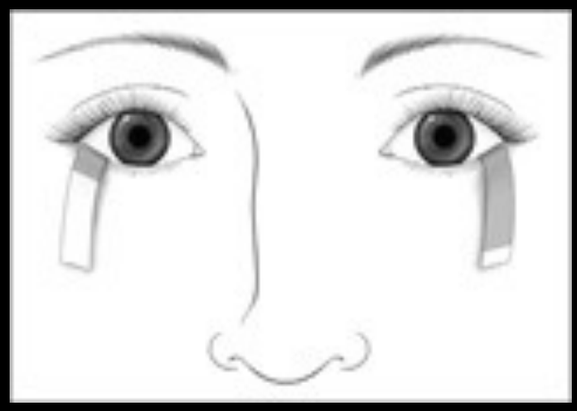


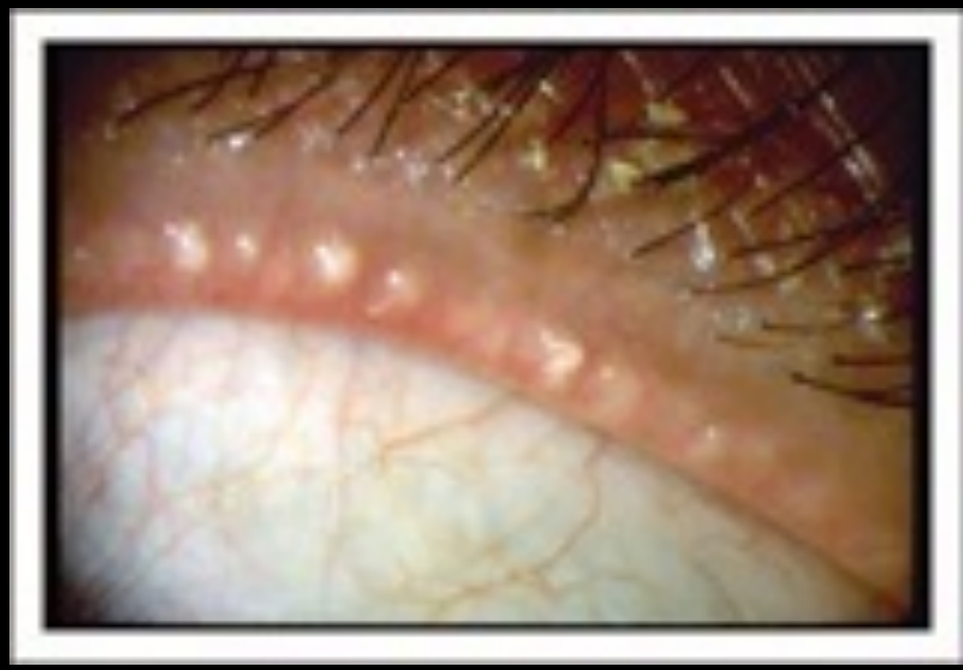
Staining of the conjunctiva with rose bengal. Image from a patient with aqueous deficiency. Rose bengal may be used to highlight areas of the conjunctiva that are abnormal or unhealthy in patients with dysfunctional tear syndrome (DTS). Moderate staining of the conjunctiva is shown with a classic pattern for keratoconjunctivitis sicca. © 1994 American Academy of Ophthalmology.

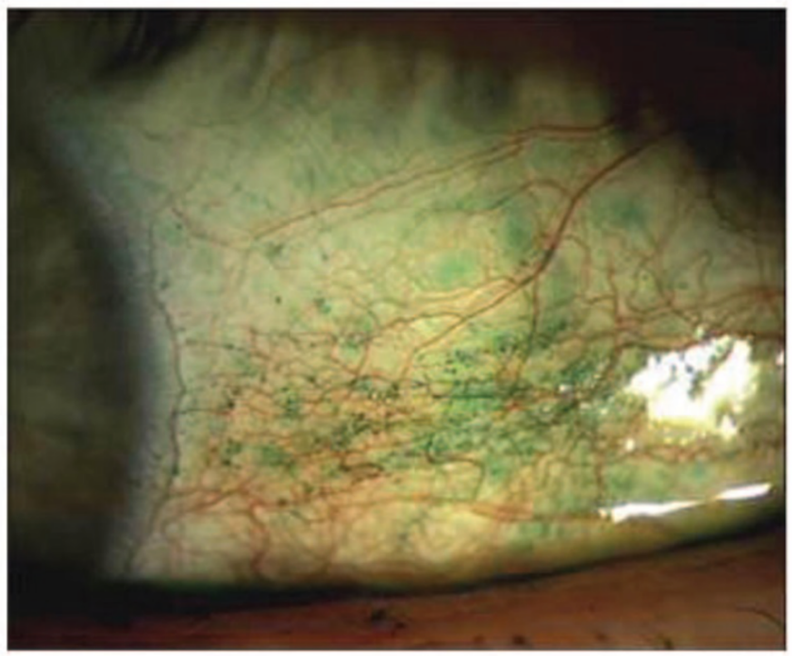
Source

Dysfunctional tear syndrome: dry eye disease and associated tear film disorders – new strategies for diagnosis and treatment

Current Opinion in Ophthalmology28:3-47, January 2017







Staining of the conjunctiva with lissamine green. Image from a patient with aqueous deficiency. Vital dyes, such as lissamine green, may be used to visualize debris in the tear film and regions of the conjunctiva that are deficient in mucin. Moderate-to-severe lissamine green staining of the temporal aspect of the conjunctiva is shown. Image courtesy of Elizabeth Yeu, MD.

Source

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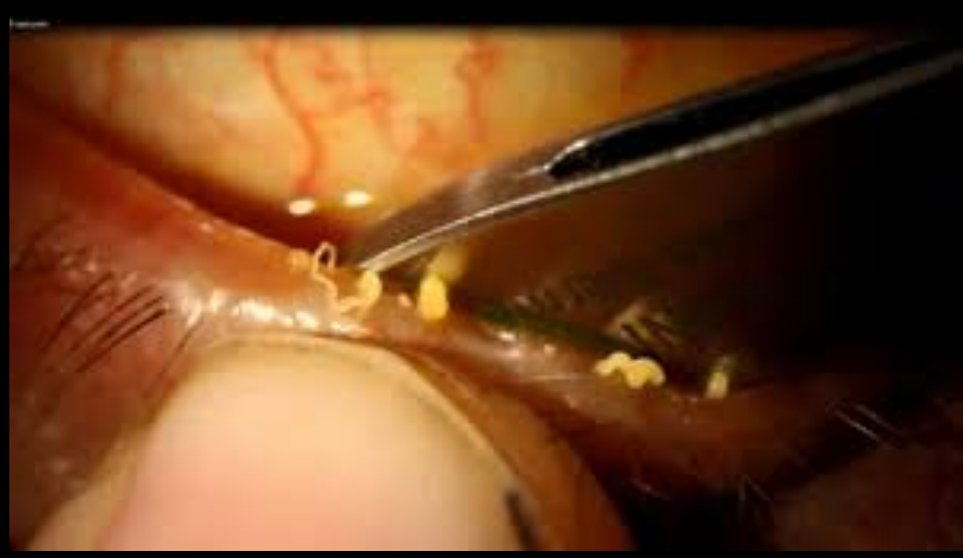
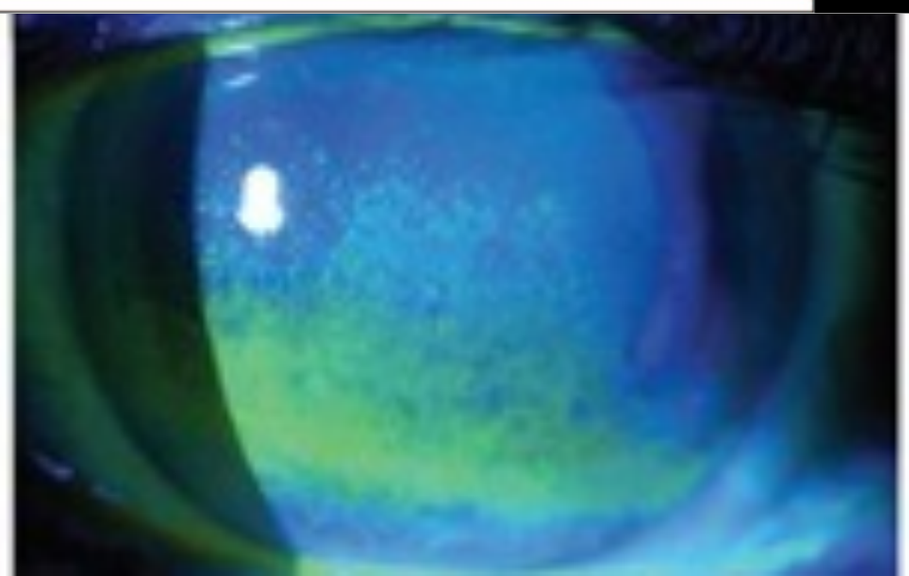




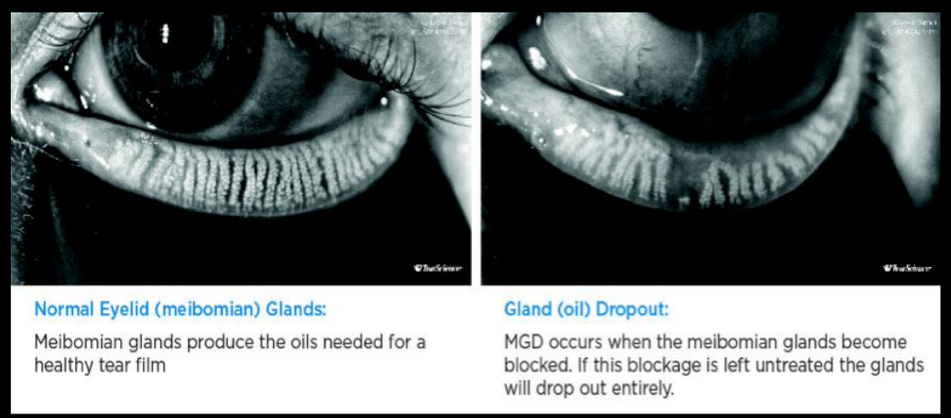
Diagnostics

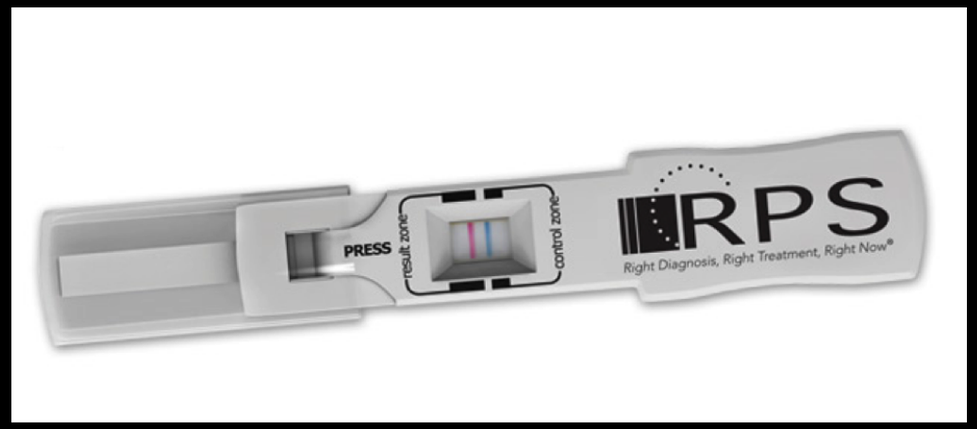
- Lipid thickness interferometry (LipiView II): looks at the lipid thickness of the central tear film, inability to view the dynamics of the entire tear film and changes over time (stability)

- Tear osmolarity (TearLab): provides one measurement (>308 mOsms/L in DED), may not be as useful as several measurements over time showing stability/homeostasis of the tear film. Can track therapeutic response, osmolarity may improve before symptoms do.

- Measuring inflammation (InflammaDry): measures MMP-9, qualitative (>40mg/mL is positive), not quantitative so difficult to determine how much it is contributing, MMP-9 increases with increase in disease activity.

- LipiView: meibography highlights meibomian gland anatomy (gland atrophy)

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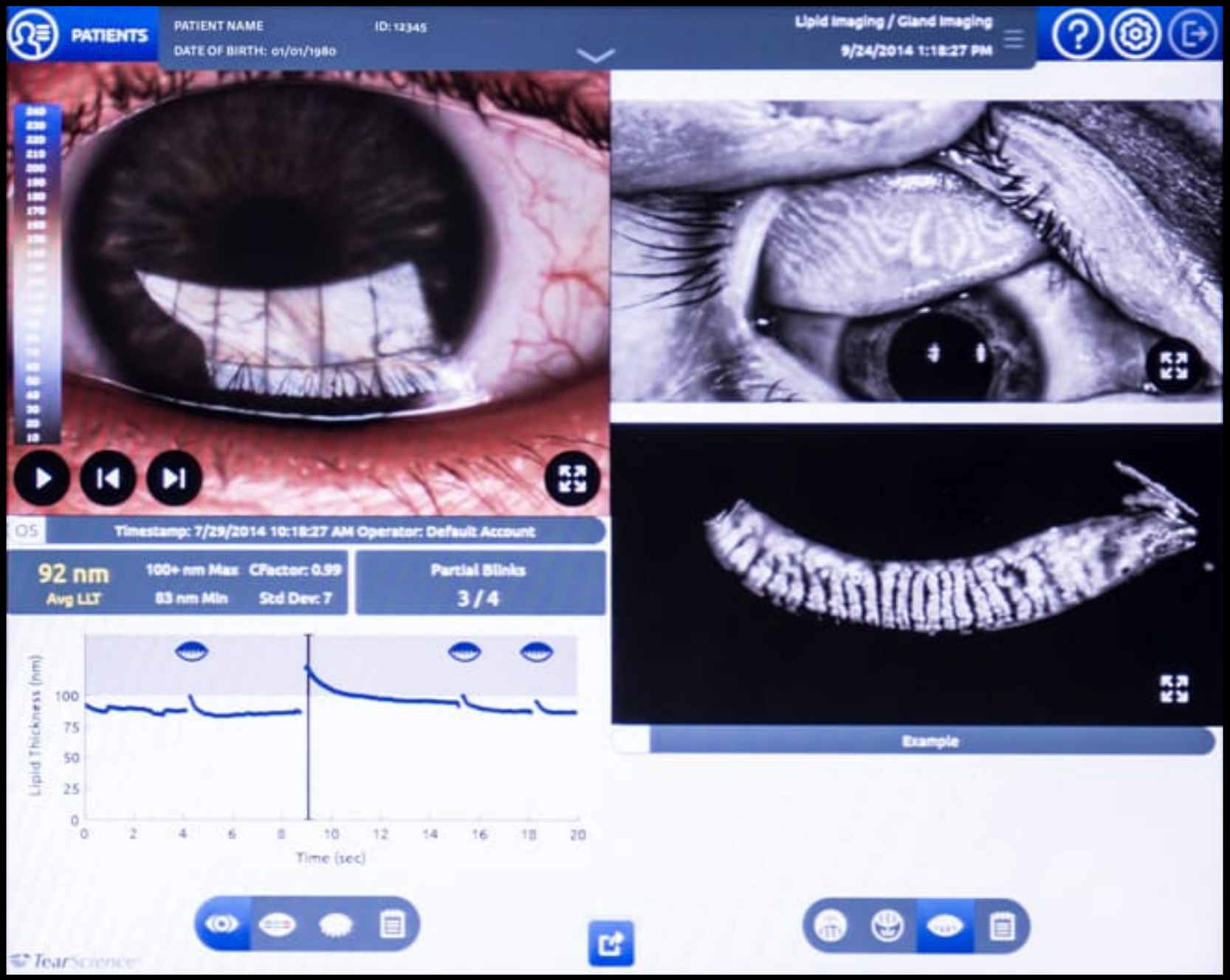
control zone
RPS
Right Diagnosis, Right Treatment, Right Now®


PATIENTS
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DATE OF BIRTH: 01/01/1980
Lipid Imaging / Gland Imaging
9/24/2014 1:18:27 PM
OS
Timestamp: 7/29/2014 10:18:27 AM Operator: Default Account
92 nm
Avg LLT
100+ nm Max
83 nm Min
CFactor: 0.99
Std Dev: 7
Partial Blinks
3 / 4
Lipid Thickness (nm)
100
75
50
25
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2
4
6
8
10
12
14
16
18
20
Time (sec)
Example
TearScience

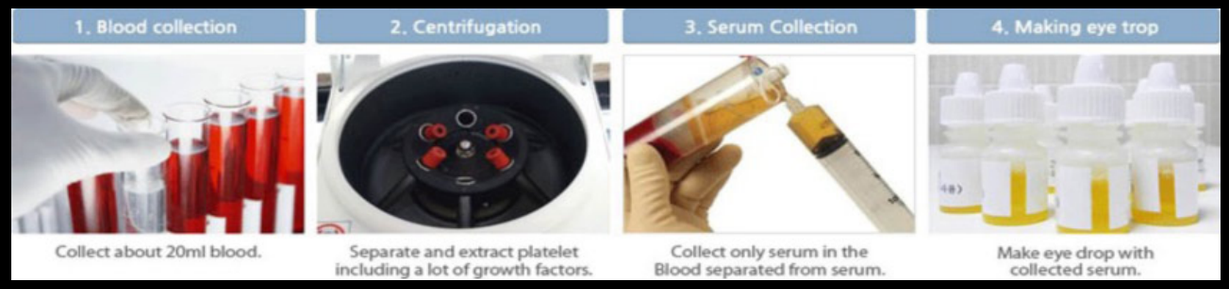
First Line Treatments

- Education!!!
- Tear supplements (drops, gel, ointment, inserts)
  - Aqueous deficiency, goblet/mucin deficiency, MGD/blepharitis and exposure related (ALL SUBTYPES)
- Omega fatty acid nutritional supplements
  - Aqueous deficiency, MGD/blepharitis
- Lid hygiene (warm compresses, scrubs, massage) to reduce bacterial load in MGD/blepharitis
  - Recent study shows dedicated lid cleansers are better tolerated and may provide improvement in MMP-9 levels and lipid quality as compared to diluted baby shampoo
- Environmental changes or changes to contributors (including changing oral meds and addressing underlying disease) for ALL SUBTYPES

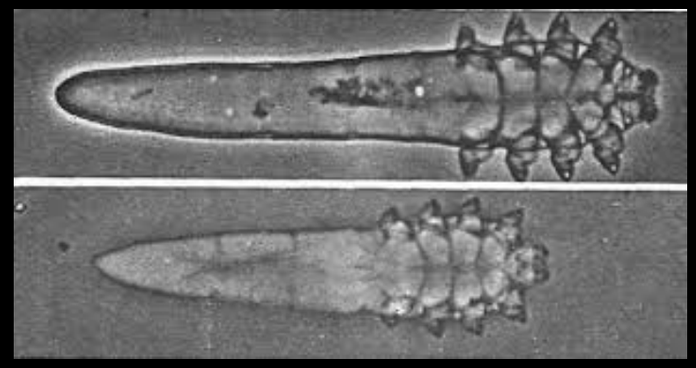
First Line Treatments

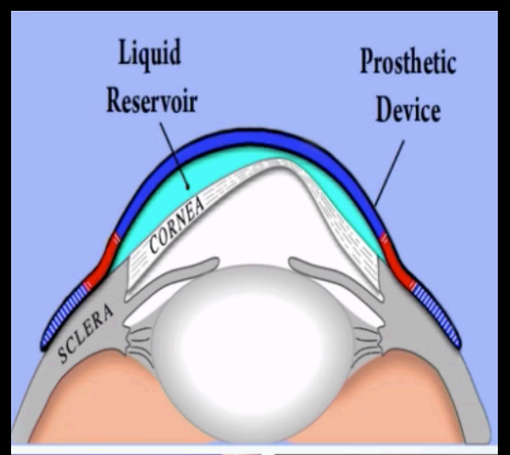
- Taping eyelids for exposure related conditions
- Moisture chamber
  - Aqueous deficiency, goblet/mucin deficiency, and exposure related
- Topical cyclosporine and topical lifitegrast, topical steroids (loteprednol and fluorometholone), topical secretagogues (not available in the U.S.)
  - Aqueous deficiency, and goblet/mucin deficiency
- Topical azithromycin or topical bacitracin/erythromycin or antibiotic/steroid
  - MGD/blepharitis

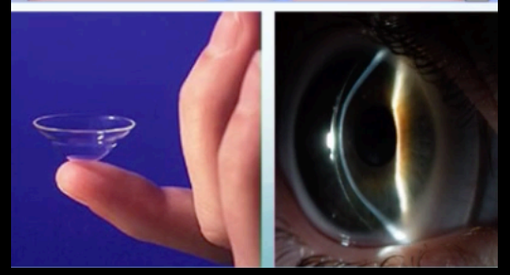
Second Line Treatments



- Aqueous deficiency
  - topical compounded medications:
    - autologous serum tears, hormones (topical testosterone improves quality of MG secretions in phase 2 trials), albumin, dapsone, tacrolimus (blocks T cells), N-acetylcysteine (mucolytic and antioxidant)
  - oral secretagogues (pilocarpine < cevimeline) for patients with Sjögren syndrome
- MGD/blepharitis
  - oral doxycycline/tetracycline or azithromycin (no level 1 evidence to support this)
  - Demodex tx: no high level evidence for use including metronidazole gel, tea tree oil, oral ivermectin
  - topical compounded medications:
    - metronidazole, doxycycline, clindamycin, dapsone, N-acetylcysteine
- Scleral RGP contact lenses or soft bandage contact lenses for all subtypes (aqueous deficiency, goblet/mucin deficiency, MGD/blepharitis and exposure related), reserved for more severe given risks

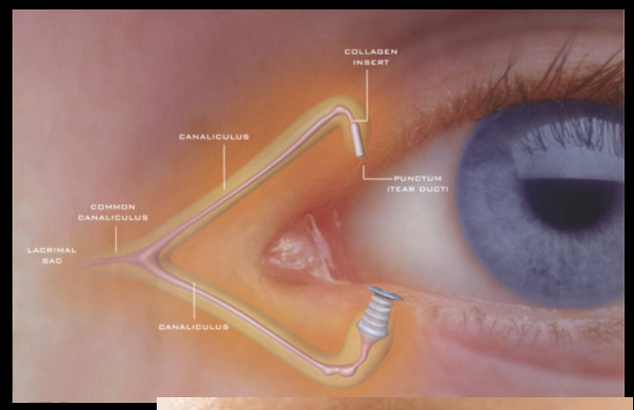


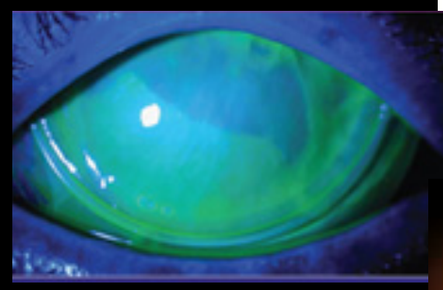


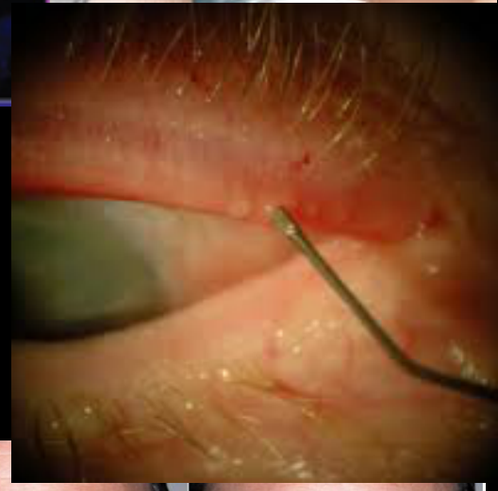


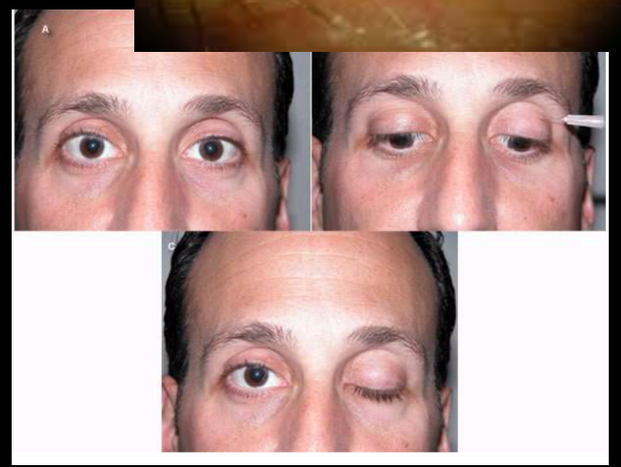
Procedural Treatments

- Aqueous deficiency:
  - punctual plugs, cautery punctal occlusion
  - amniotic membrane (PROKERA/PROKERA SLIM, AmbioDisk)
- MGD/blepharitis:
  - thermal pulsation/lid massage and expression (Lipiflow, MiBo Thermoflo, or intense pulsed light laser)
  - debridement of lid margin (keratinization over MGs)
  - Meibomian gland probing
- Exposure:
  - eyelid surgery (correction of malposition and tarsorrhaphy), “botox tarsorrhaphy”









Anti-inflammatory Therapy: Mechanism of Action

- Corticosteroids: multiple mechanisms of action, good for induction and acute exacerbations
    - inhibit cytokine and chemokine production, decrease MMP synthesis, decrease lipid mediators of inflammation (prostaglandins), decrease T cell adhesion molecules and stimulate lymphocyte apoptosis
- Cyclosporine
    - inhibit T cell activation genes, leads to decrease in cytokines (IL-6) and T cells, and increase in goblet cell density (0.05% cyclosporin FDA approved for DED in 2002- Restasis)
        - Recent approval for 0.09% cyclosporin (Cequa) 8/2018, nanomicellar formulation for better penetration (small size and better solubility)
- Lifitegrast
    - inhibit T-cell inflammation and cytokine release by blocking the binding of 2 cell surface proteins (LFA-1 and ICAM-1). It inhibits the interactions of the surface proteins, which is thought to block the cycle of T cell mediated inflammation (approved for DED in 2016)
- Tetracyclines (and derivatives-doxycycline and minocycline):
    - decrease activity of collagenase, inhibit MMP expression, decrease cytokine production

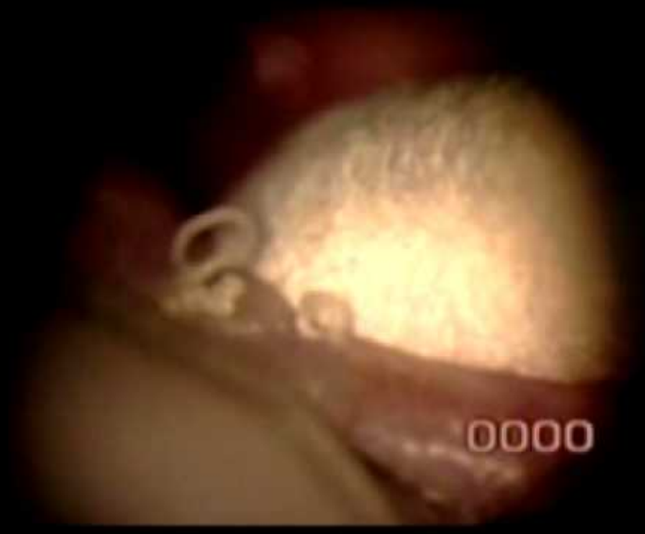
Anti-inflammatory Therapy: Mechanism of Action

- Essential fatty acids: omega-3 fatty acids (DHA and EPA) and omega-6 (GLA) block production of cytokines and prevent T cell proliferation

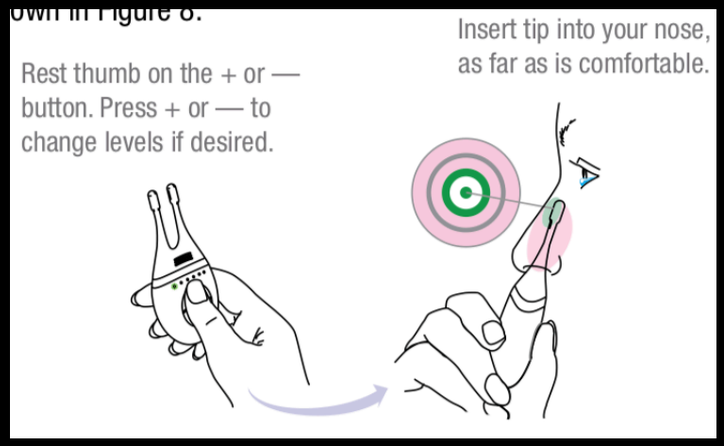
- Do they really help?
  - April 2018 DREAM study (Dry Eye Assessment and Management trial) found omega-3 is no better than placebo (olive oil)
- Both placebo and omega-3 were helpful
- This was a large subset with heterogeneous subclasses of dry eye (cannot treat different dry eye patients the same, need a more tailored approach)
- There are many other papers showing improvement in either symptoms or testing parameters, however many are contradictory, this is a controversial topic and more research and individualized patient treatments are needed

Non-medication Based Treatments

- Plugs: avoid in patients with inflammation or with allergies (“drugs before plugs”)
    - Could prolong pro-inflammatory cytokines on the ocular surface
- Lipiflow: thermal pulsation system for treatment of meibomian gland dysfunction
    - Allows effective MG expression to remove any gland obstruction and improve functionality
    - Effects last for up to 12 months or more
- IPL (intense pulsed light laser 500-1200nm) with manual expression of meibomian glands
    - First used 15years ago for MGD



Non-medication Based Treatments



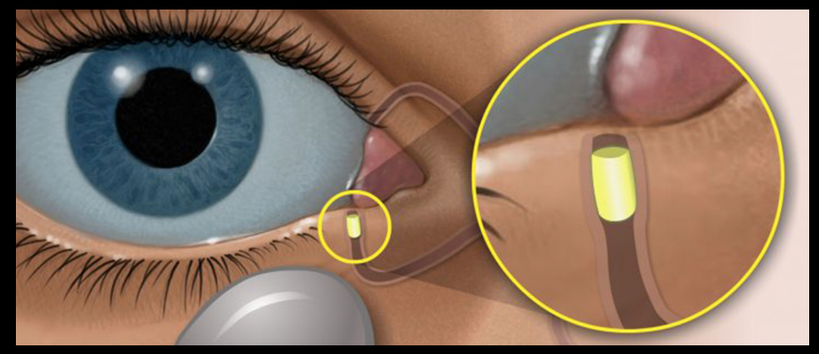
- True Tear: an intranasal tear neurostimulator
  - indicated for severe dry eye (FDA approval 2017)
  - handheld device, delivers tiny electrical pulses inside the superior nasal cavities, stimulates an ophthalmic branch of the trigeminal nerve fibers in the nasal cavity (anterior ethmoidal nerve/nasociliary nerve)
    - Nasolacrimal reflex: upregulates tear production with stimulation of nasal mucosa
- used daily 2-4 times a day, less than 1 min (possible that the more you use it the less frequently you need it due to recovery of the ocular surface in longer term study)
- stimulates all 3 layers of the tear film (aqueous, mucin and meibum)

Treatments on the Forefront

- MIM-D3: a TrkA receptor agonist that acts on neurotransmitters (phase 3 trials), promotes survival of neuronal cells (may improve corneal sensitivity), increases mucin secretion

- EBI-005: an interleukin-1 receptor inhibitor administered as a topical drop, decrease in cytokines (initial phase 3 in 2015 poor response)

Treatments on the Forefront



- Dextenza: a sustained-release dexamethasone loaded punctual plug, resorbs slowly over 30days. FDA approved December 2018 for post-operative ocular pain/inflammation.

- Rebamipide: a mucin stabilizer and secretagogue, increases mucin secretion, decreases corneal and conjunctival damage, decreases cytokines, approved in Japan (Failed approval by the FDA after phase 3 trial)

Treatments on the Forefront

- Cross linked hyaluronic acid (HA) eyedrops: promote epithelial wound healing, possible decrease in cytokines (being researched)

- PCA (5-oxo-2-pyrrolidinecarboxylic acid) with or without HA: artificial tears, enhanced protection may be due to osmoprotective effects -offsets hyperosmolarity from DED (being researched)

- iLid TearCare system: software controlled, wearable eyelid technology that directs heat to meibomian glands to promote natural meibum expression, in-office procedure (coming in 2019)

Treatments on the Forefront

- Amniotic membrane extract eye drops: promotes corneal regeneration, prevents apoptosis, reduction in inflammatory cytokines (on the market, not currently FDA regulated)

- Diquafosol: a uridine nucleotide analog and agonist of P2Y2 receptor, promotes aqueous tear secretion and mucin secretion. Approved in Japan and South Korea. (Failed approval by the FDA after phase 3 trial)

- Thymosin-β4 (RGN-259): naturally occurring protein that promotes corneal surface healing, promotes corneal epithelial cell migration, decreases inflammation and has anti-apoptotic activities. (completed phase 2 trial, phase 3 next)

Complementary Treatments

- Acupuncture: less than 3 times a week for at least 1 month on BL1, ST2, TE23, and Ex-HN5 acupoints
    - Several good studies with improvement in symptoms and increased tear production (artificial tears as control), 1 RCT used sham needle with no difference.
- Honey: bee products have shown antibacterial, anti-inflammatory, antioxidant and wound healing properties (safety in phase 1 trial for Manuka honey cyclopower micro-emulsion eye cream)
- Breastmilk: common natural remedy for ocular ailments in many cultures, minimal evidence for dry eye use

Barriers To Care

- Expense!
    - Diagnostic testing, procedural treatments, anti-inflammatory drops, neurostimulation unit…even artificial tears
- Compliance: poor compliance with lid hygiene, warm compresses, drops, lifestyle changes
- More research needed for many current treatments to achieve better guidelines

Odds and Ends

- Treat DED prior to cataract surgery!
  - measurements more accurate
  - will likely have increase in DED post-op
- Now we see DED in younger patients (increase in screen time)
  - easier to treat disease earlier (ramps up over years or decades)
- Treat any risk factors and contributors! Address underlying diseases and environmental/extrinsic factors for all DED subtypes!

Resources for Patients

- NotADryEye.org
- nei.nih.gov/health/dryeye
- MyDryEyes.com
- sjogrens.org

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Thank you!
Any questions?