Communication is Key to Successful Management of Ocular Surface Diseases

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To Be or Not To Be Adherent

What Would You Do?

Smile?

Laugh?

Say
Nothing?

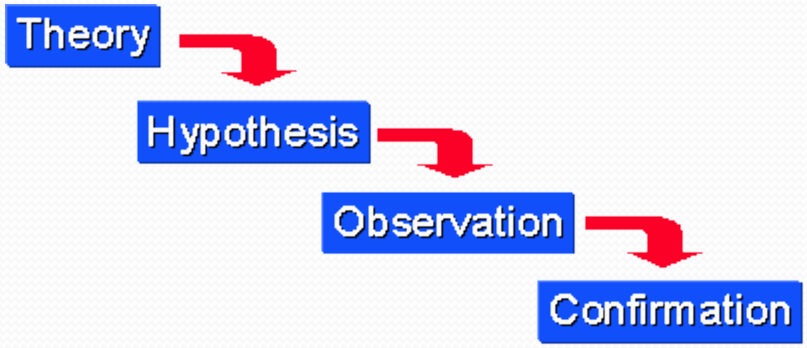
Instruct?

Emphathize?

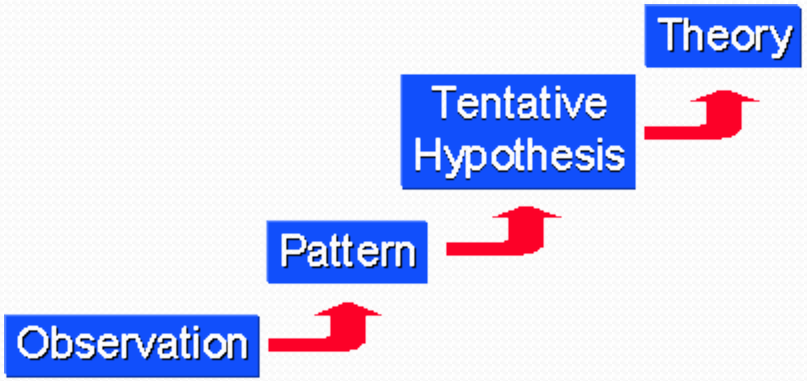
Verbal/Nonverbal Cues

- Sizing Up
- The Handshake
- Salutation
- Eye Contact
- Down to Earth Analogies
- Closing the Loop
- Call to Action

Deductive vs. Inductive



Are You Here?



Or There?

Are You Open or Closed?

- Are you feeling better today?
- Can I help you?
- Should I date him?
- Is Optometry your favorite job?
- Is that your final answer?
- How did you and your best friend meet?
- What is your favorite memory as a child?
- How did you book those tickets?
- What did you learn by the end of this meeting?

The Power of "Because"

- Harvard Research Study by Ellen Langer in 1978
- Syntax matters and Quantity does make a difference!

QUESTION:	CONV. RATE:
Excuse me. I have 5 pages. May I use the Xerox machine?	60%
Excuse me. I have 5 pages. May I use the Xerox machine because I'm in a rush?	94%
Excuse me. I have 5 pages. May I use the Xerox machine because I have to make some copies?	93%

QUESTION:	CONV. RATE:
Excuse me. I have 20 pages. May I use the Xerox machine?	24%
Excuse me. I have 20 pages. May I use the Xerox machine because I'm in a rush?	42%
Excuse me. I have 20 pages. May I use the Xerox machine because I have to make some copies?	24%

Langer, E., Blank, A., & Chanowitz, B. (1978). The mindlessness of Ostensibly Thoughtful Action: The Role of "Placebic" Information in Interpersonal Interaction. Journal of Personality and Social Psychology, 36(6), 635-642.

Because = Compliance

- 1. **Always give a reason**. Human brain is wired to react when it hears *because*. It is a magical word. It is an automatic trigger for compliance, and in many cases a person stops paying attention to what comes after they hear *because*.

- 2. **Share your mission** – add what is the bigger reason why you do what you do. Doing so will make people feel like they are contributing to that mission and doing more for the greater good.

The Cost of Non-adherence

- In the United States, avoidable healthcare costs add up to $213 billion, of which $105 billion is due to medication non-adherence, according to the **Express Scripts 2013 Drug Trend Report**.
- Non-adherence causes 30-50 percent of treatment failures and 125,000 deaths annually.[1]
- Medications are not continued as prescribed in about 50 percent of cases, according to a 2013 **Centers for Disease Control and Prevention (CDC) presentation.**
- Nearly 50 percent of Americans have one or more chronic conditions that require prescription medications, according to the **CDC.**
- Medication adherence is higher among patients who see the same healthcare provider each time they have a medical appointment. In this group, the average adherence is 81 percent, according to "Medication Adherence in America: A National Report Card," a recent report from the **National Community Pharmacists Association.**
- For some classes of medication, up to 30 percent of prescriptions are never filled by the patient, according to the **Network for Excellence in Health Innovation (NEHI).**
- Patients receive 3.4 more refills per prescription in a 12-month period when their refills are synchronized, according to the **National Community Pharmacists Association.**

[1]Smith D, Compliance Packaging; a patient education tool, American Pharmacy, Vol. NS29, No 2, February 1989.
http://www.fda.gov/Drugs/ResourcesForYou/HealthProfessionals/ucm470165.htm

Adherence Strategies

- Empowering Staff to actively educate
- Time of Day administration
  - Meal Times Statistics and Bottle Cap Colors
- Coupon or Savings Programs
  - Industry Support Hotlines
- Motivational Interviewing
  - Social Contracts
- Brand Medication Empathy

The patient journey, enhanced.
At-home, in-clinic.

- CheckedUp is an interactive patient engagement platform that seamlessly provides disease and surgical education to your patients, makes patients aware of practice specific offerings to manage or treat their condition, and captures patients' preferences of their specific options.

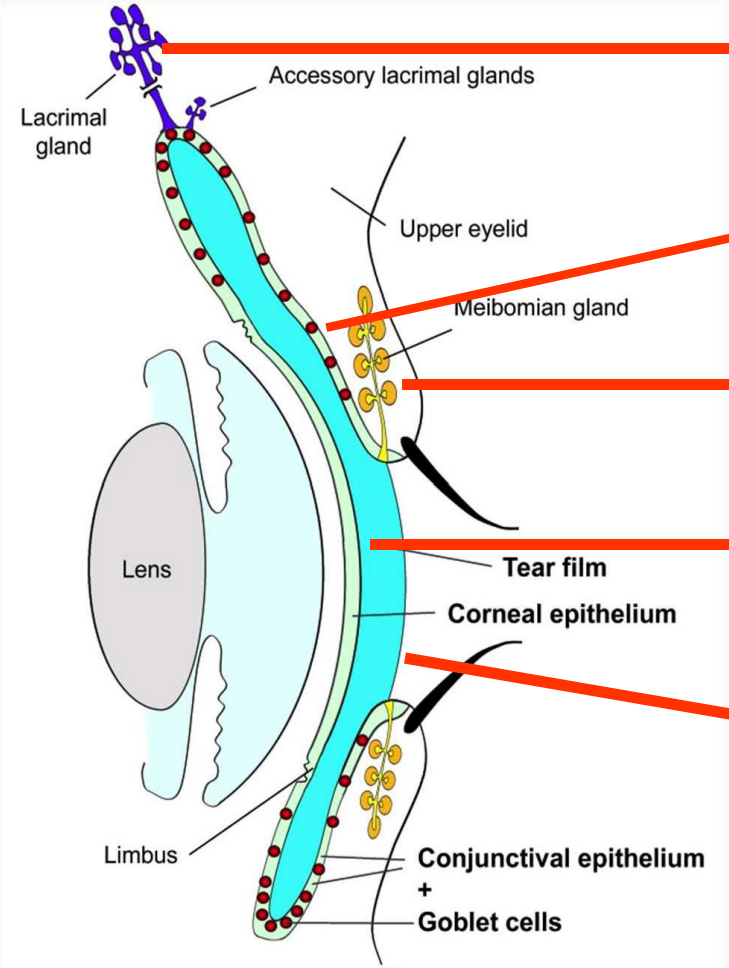
Enhance the patient experience with memorable conversations

- Rendia blends stunning clinical artwork with interactive technology to improve patient outcomes
- Customize presentations, share content, and track engagement with Rendia
- Educate beyond the visit

Tailor to your workflow!

Dry Eye Disease: The Most Confounding and Engaging Condition Ever

The Ocular Surface



Lacrimal glands

Conjunctival epithelium with goblet cells

Meibomian glands

Corneal epithelium

Tear Film

Ocular Surface Inflammation

- The ocular surface is a complex structure responsible for visual function and for protection of the eye against external insults.
- Comprising a variety of disorders on cornea, eyelid, conjunctiva, lacrimal apparatus and tear film, there are countless triggers of ocular surface inflammation.

- Preserve corneal integrity and transparency.

Walk a Day in *Their* Shoes

The 1-2-3 Rules for Identifying, Diagnosing, & Treating.

- Rule #1: Similar to the subjective 20/20, never underestimate the patient's level of discomfort.
- Rule #2: Use that noodle and sleuth in office clues.
- Rule #3: Create a protocol and invest in 1 Point of Care test that you will use consistently as a metric.

Predisposing factors

- Age
- Gender
- Environment
- Medications
- CL Wear
- Refractive or Cataract surgery
- Trauma
- Anterior Segment Disease
  - ABMD
  - CCHal
  - Blepharitis
  - Allergy
- Systemic Disease
  - Diabetes
  - Thyroid

Gender

- Sjögren's: Dry eye is characterized by a *triad* of dry eye, dry mouth, and associated autoimmune disorders.
- Prevalence
  - – 0.4%
  - – 85% women
  - Strong relationship (46%) to non-Hodgkin's Lymphoma

- Sjö Test (Valeant/B+L)
  - In Office or QuestDx/LabCorp

Sjö Test Diagnostics

	Biomarker	Diagnostic Characteristics
Novel, proprietary	**Salivary Protein-1 (SP-1, IgA, IgG, IgM)**	**Provides high specificity and sensitivity for early Sjögren's syndrome[7]**
	Carbonic Anhydrase (CA-6, IgA, IgG, IgM)	**Offers additional sensitivity for an early diagnosis[7]**
	Parotid Secretory Protein (PSP, IgA, IgG, IgM)	**Expressed early in disease course[7]**
Traditional	SS-A (Ro)	Expressed in about 70% of patients; typically appears later than novel biomarkers[5,7]
	SS-B (La)	Less frequently expressed than Ro; typically appears later than novel biomarkers[5,7]
	Antinuclear Antibody (ANA) by HEp-2	Expressed in about 60% of Sjögren's syndrome patients[1]
	Rheumatoid Factor (RF) Levels (IgA, IgG, IgM)	Found in many rheumatic conditions but is not unique to Sjögren's syndrome[1]

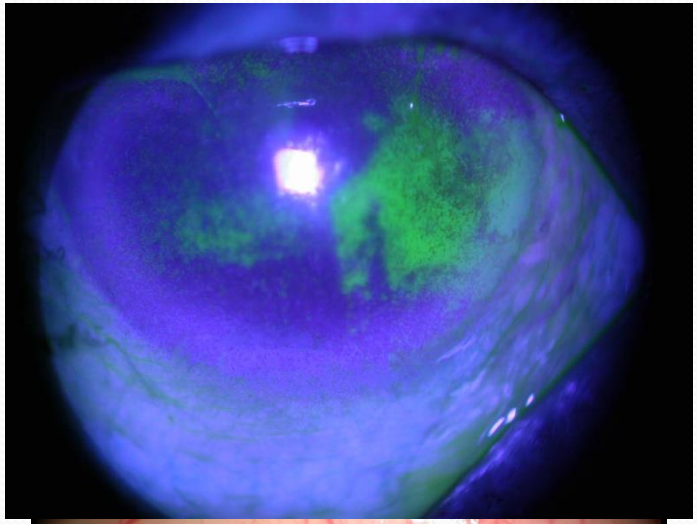
Environment

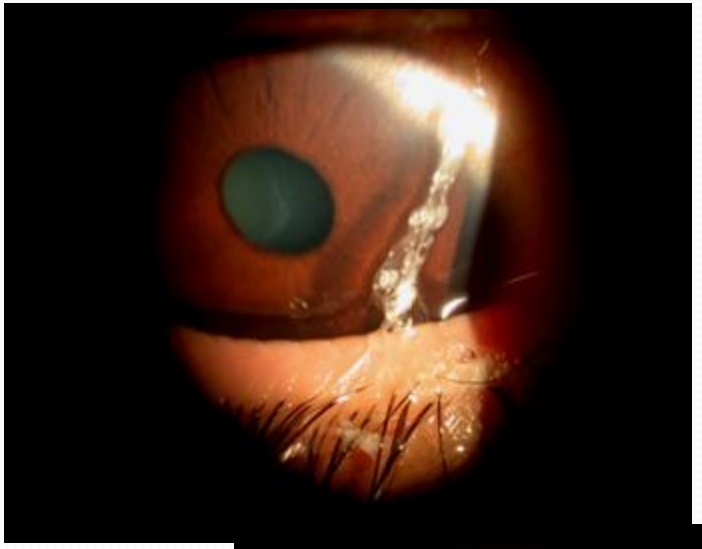
- Air conditioners or heaters
- Airline travel
- Winter months, allergy season
- Ceiling or Oscillating Fans
- Exogenous irritants (smoking or general pollution)
- Reading time
- Digital device use (That's right, the device you are texting on right now!)

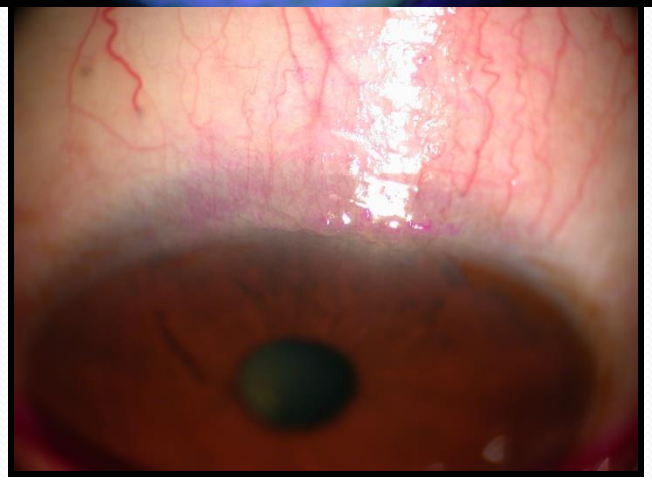
Symptoms of Dry Eye

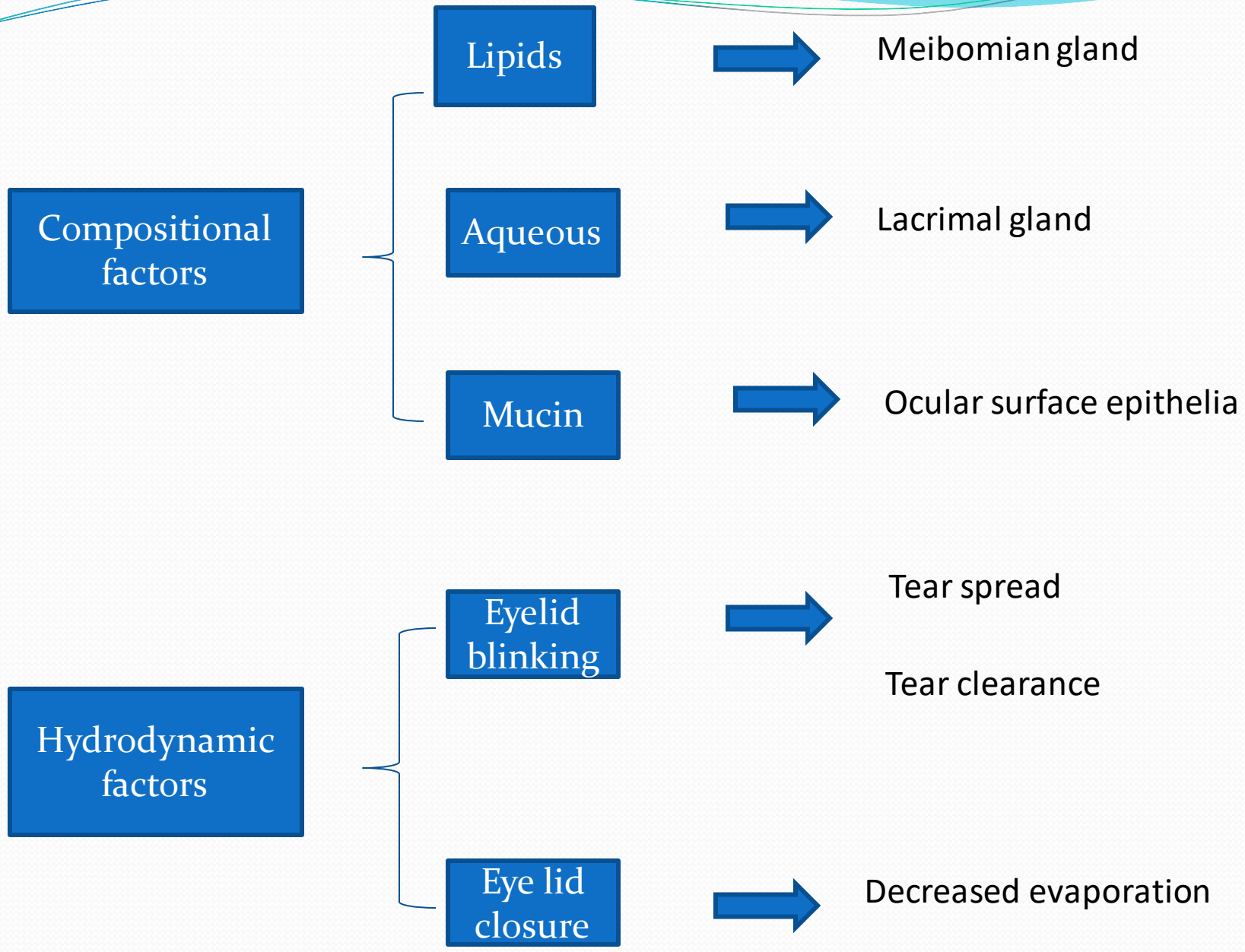
- Burning
- Stinging
- Transient blur
- Dryness
- Photophobia
- Epiphora
- Blurred vision
- **Contact lens intolerance**
- Redness
- Foreign body sensation
- Grittiness
- Increased blink rate

Dry Eye Can Cause Serious Visual Loss








Compositional factors
Lipids
Meibomian gland
Aqueous
Lacrimal gland
Mucin
Ocular surface epithelia
Hydrodynamic factors
Eyelid blinking
Tear spread
Tear clearance
Eye lid closure
Decreased evaporation

So, What is Dry Eye Disease?

- **Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface**

The Ocular Surface / April 2007, Vol. 5, No. 2 / www.theocularsurface.com

Two Types of Dry Eye

- **Aqueous Deficient dry eye is a disorder in which the lacrimal glands fail to produce enough of the watery component of tears to maintain a healthy eye surface**

- **Evaporative dry eye may result from inflammation of the meibomian glands. These glands make the lipid of tears that slows evaporation and keeps the tears stable**

**The National Eye Institute (NEI)*

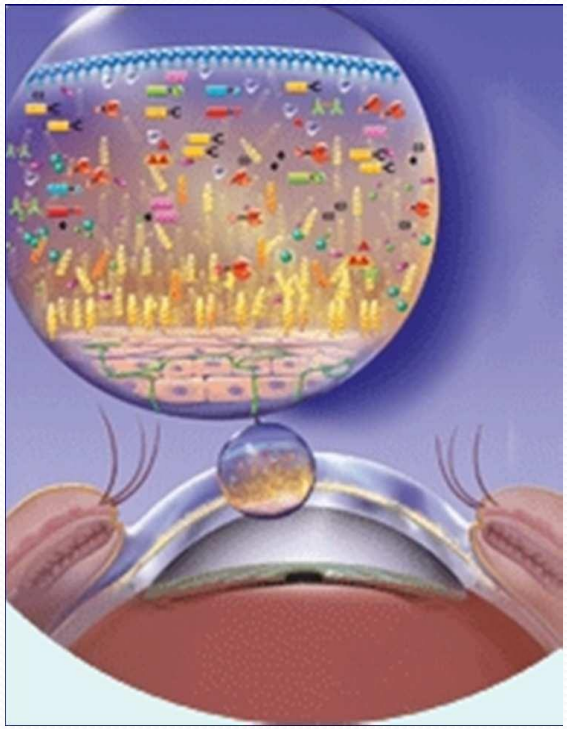
Or is it 3 Types?

- Between signs and symptoms, there are both literature and clinical experience suggesting the 2 recognized types are blended in many cases.

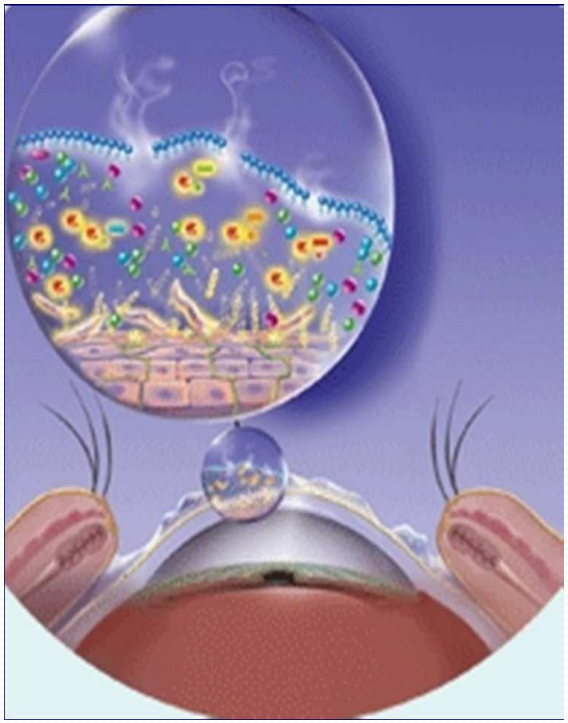
- In my practice, we make our best effort to label the cases with a support reason(s) for DED
  - ie. Aqueous Deficient Dry Eye OU due to Medication (Beta Blocker/SSRI)
  - ie. Evaporative Dry Eye OU due to Blepharitis/MGD
  - ie. Aqueous Deficient/Evaporative Dry Eye OU due to early menopause/Blepharitis/MGD/CChal

Inflammation in Dry Eye

Healthy tear film



Dry eye



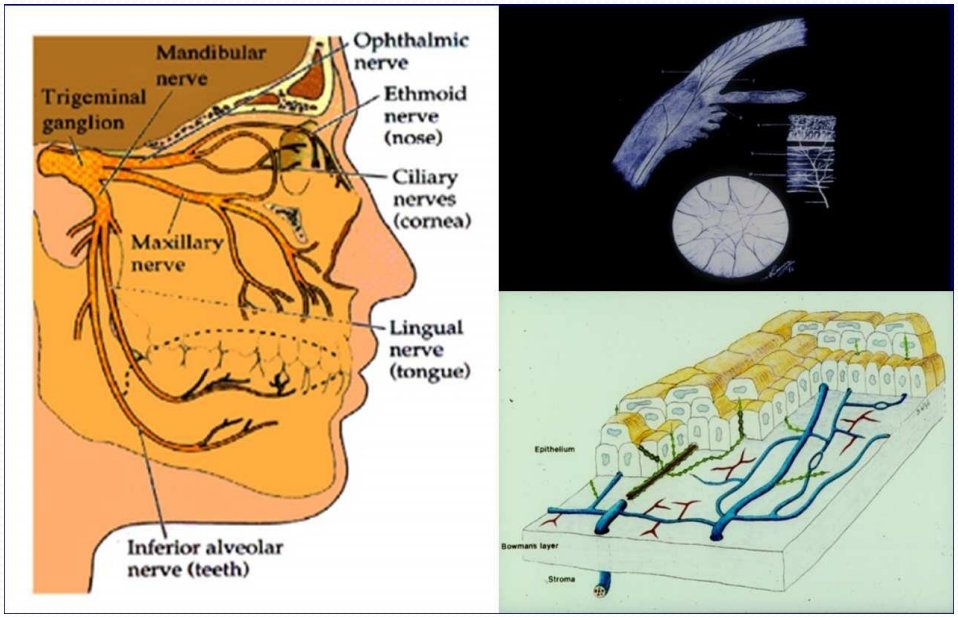
Pro-inflammatory Mediators in tears are the the main actors of DED-related events

What if there was a 4th Type?

Inflammation…… ……Chronic Pain

Corneal Innervation

- Corneal sensory innervation is the richest of the human body (100+ times more than than the tooth pulp)



- Three types of sensory nerves: mechanic (20%), chemical (70%), and cold fibers (10%).

Neurogenic Inflammation

- Inflammation that results from the release of substances from primary sensory nerve terminals.

- These neuromediators act on target cells and exert their biological activity on MC and immune cells to sustain inflammation (Richardson 2002).

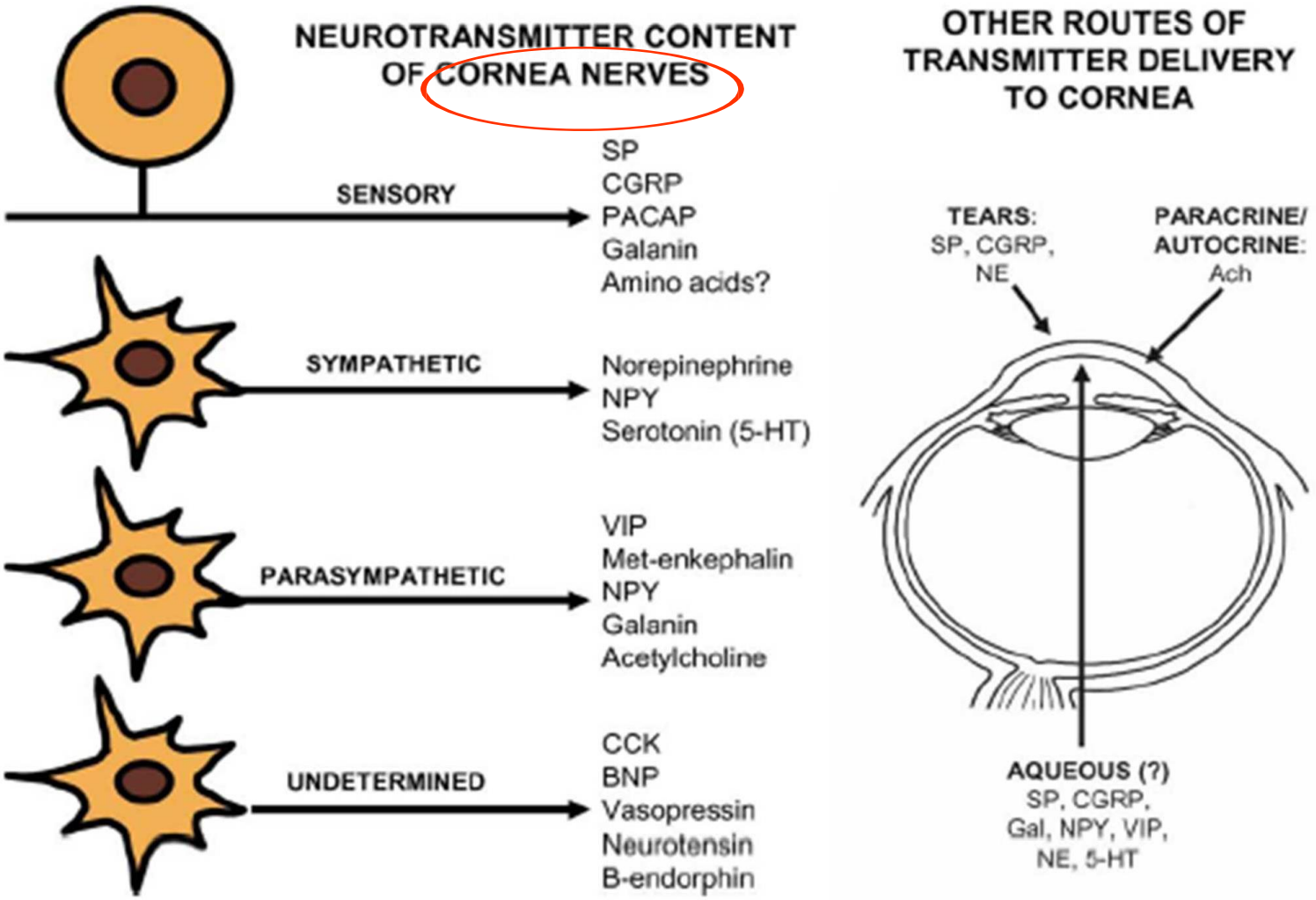


Fig. 7. Neurochemistry of the corneal innervation and the pathways by which nerve transmitter substances reach the cornea.

The neuropeptides substance P (SP) and Calcitonine gene-related peptide (CGRP) are considered to be the major mediators of neurogenic inflammation and pain.

Bornes 2001, Groneberg 2004

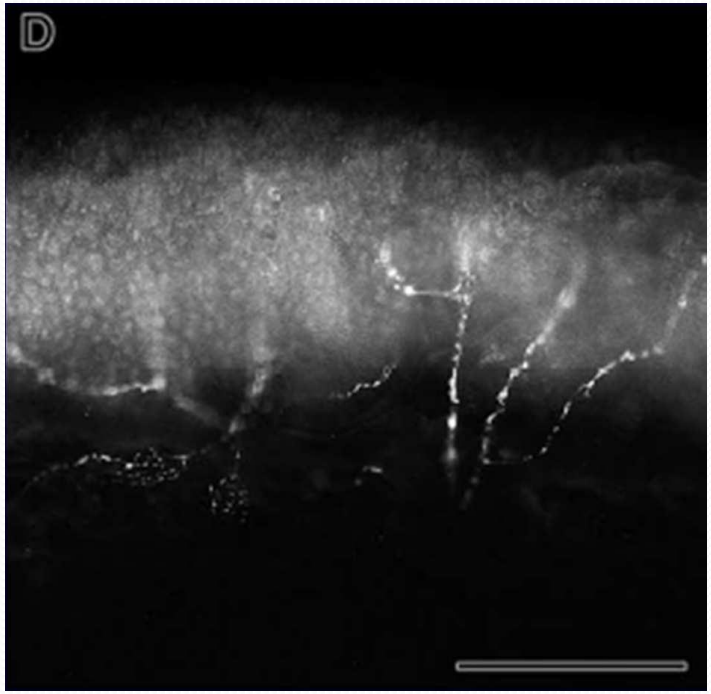
Substance P (SP)

- Substance P induces pain, vasodilation, increase in vascular permeability, stimulation of mast cell, B-T lymphocytes, chemotactant for Eosinophils. (Lambiase et al 1998, 2013)

- Substance P is produced by eosinophils, monocytes, macrophages, lymphocytes, and dendritic cells. (Lai 1998)

Substance P (SP)

- Is present in the cornea in physiologically relevant concentrations
- Its is a 11 amino acids peptide generally associated with intense, persistent, or chronic pain.



Substance P (SP) positive nerve fibers

L.J. Müller et al. / Experimental Eye Research 76 (2003) 521–542

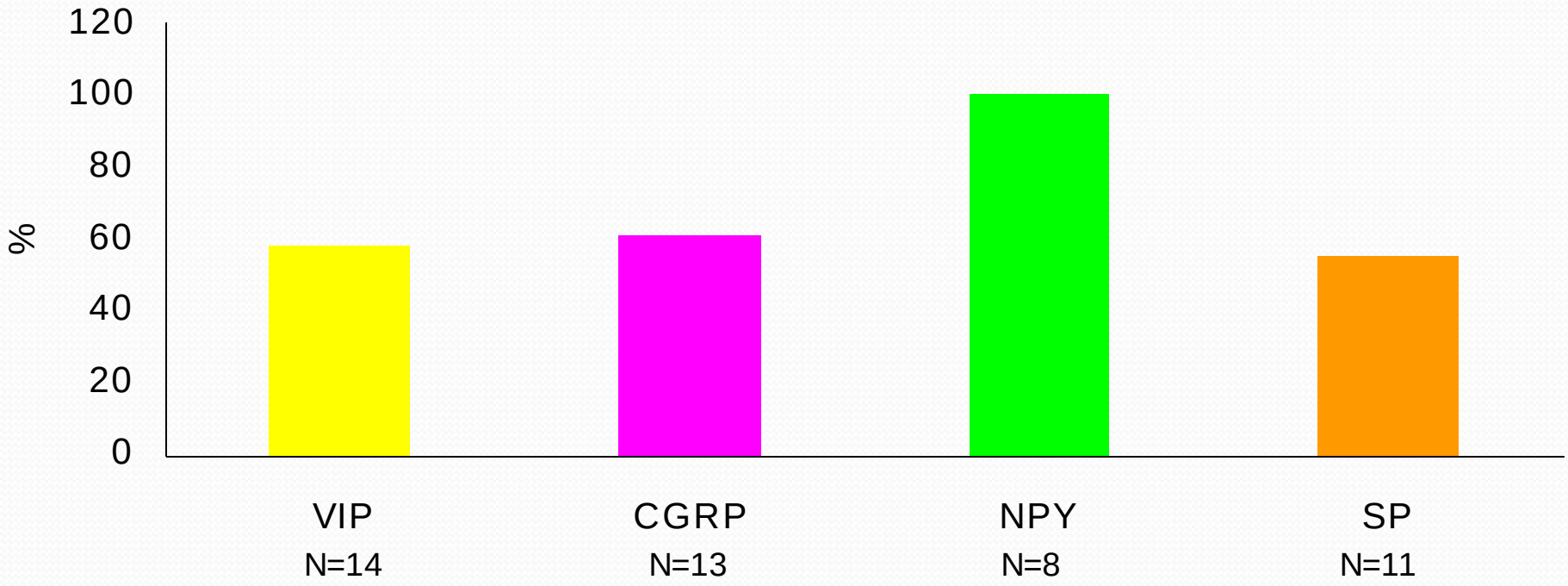
Substance P and Pain

- Nociceptors in the damaged area initiate a sensation of pain.
- These receptors are stimulated after damage due to a release of chemicals to which they are sensitive. In the cornea, these receptors are primarily *chemical* sensors, but they also respond to *mechanical* and *thermal* stimulation.
- After stimulation, they send receptor potentials, which in turn trigger afferent action potentials.

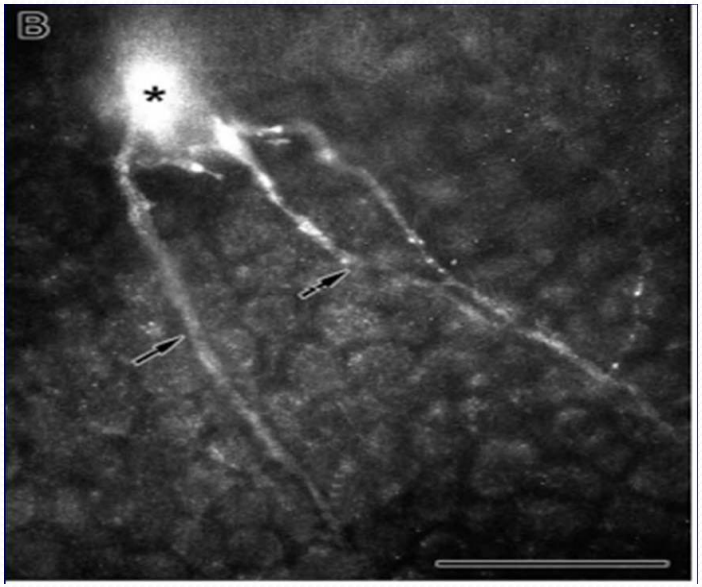
What's the Connection?

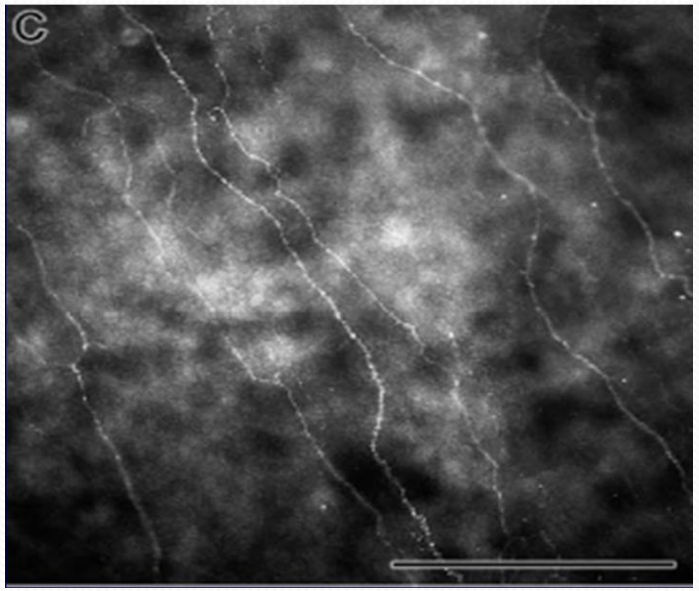
- It's not just Substance P in the tears.

(VIP=Vasoactive intestinal protein, CGRP= Calcitonine Gene-Related Protein, NPY= Neuropeptide Y)



Dry Eye is a Chronic Pain Disorder

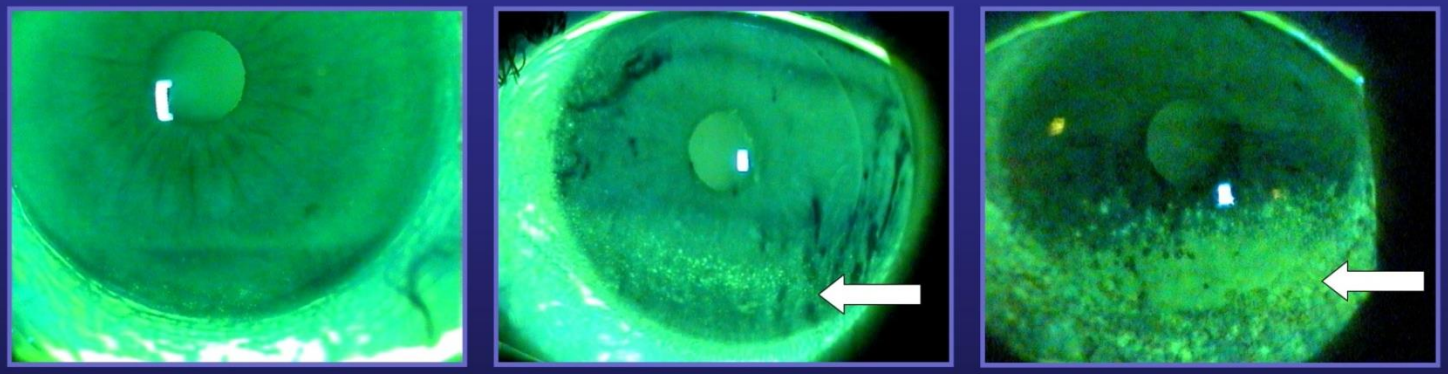




CGRP positive nerve fibers in the subbasal plexus

L.J. Müller et al. / Experimental Eye Research 76 (2003) 521–542

Classification for Treatment



Moderate → Severe

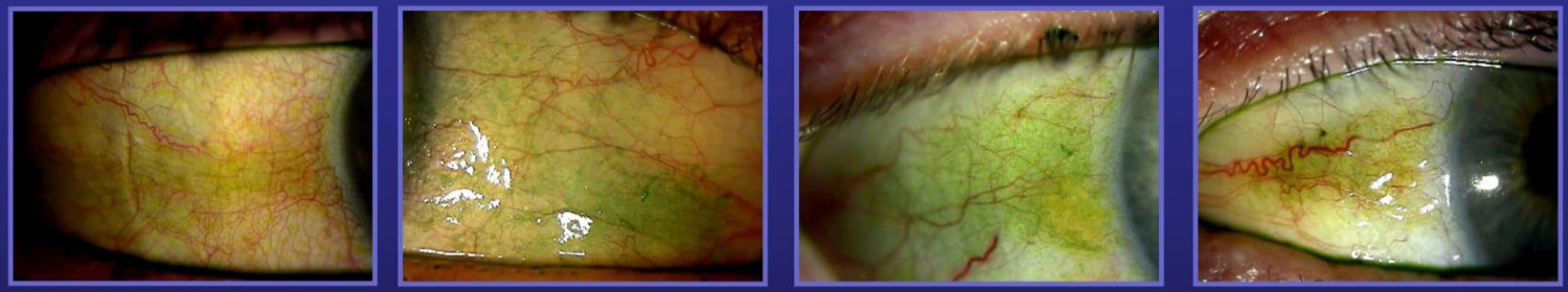
Level 2[1] → Level 3,4[1]

- Lid pattern staining is evident in the moderate and severe examples

1. Behrens et al. *Cornea*. 2006.

Images provided by Michael Belin MD, FACS; Albany Medical College.

Lissamine Green

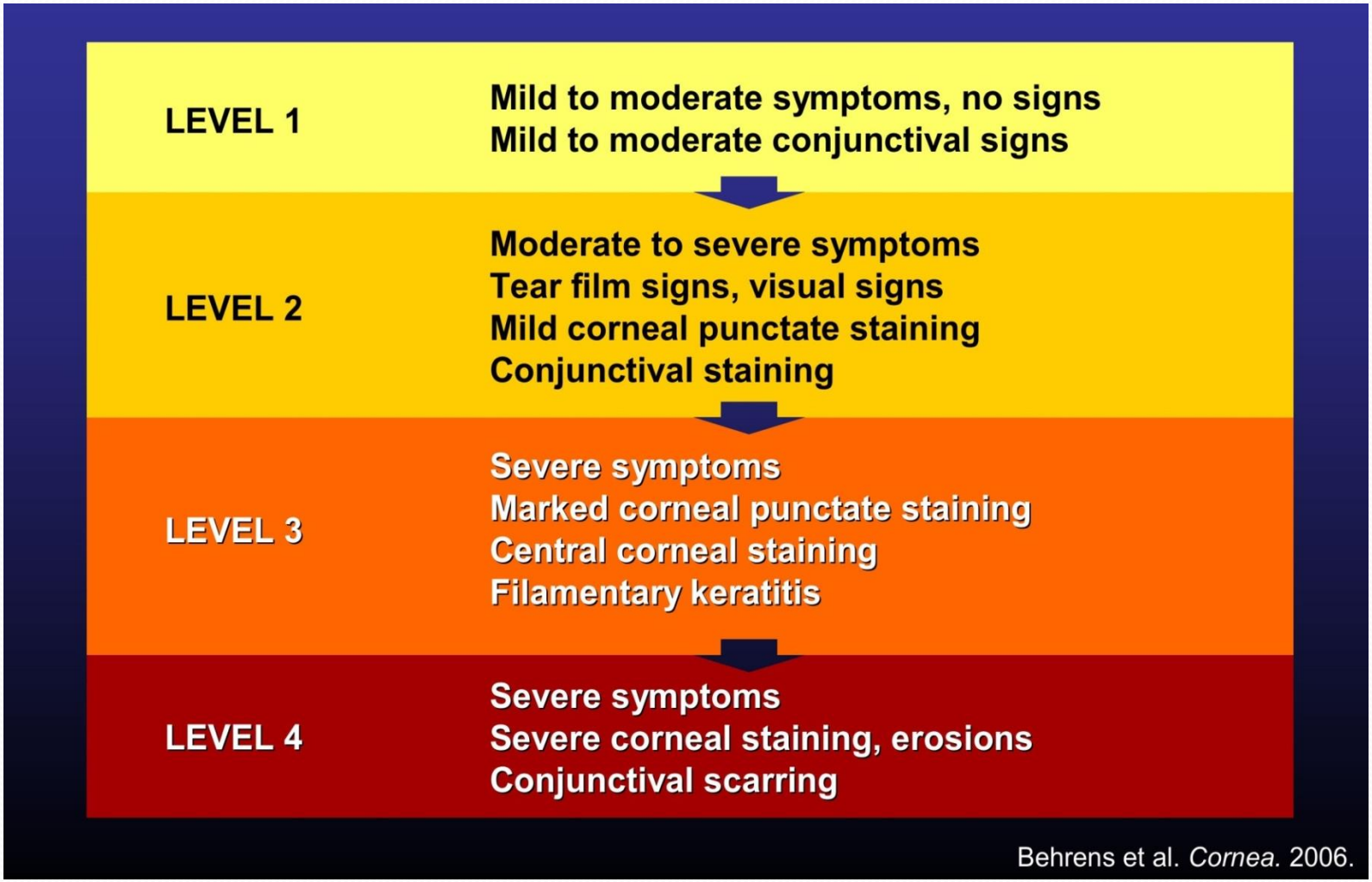


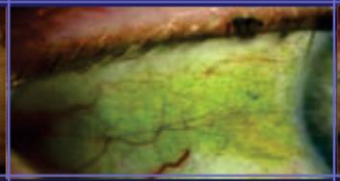
Mild | Moderate | Moderate/Severe | Severe

- Dye available only as impregnated strips
  - Less irritating than rose bengal

Chodosh et al. *Invest Ophthalmol Vis Sci.* 1994.
Images provided by Michael Belin MD, FACS; Albany Medical College.

Delphi Severity Levels



Dry Eye Severity Level	1	2	3	4
General Symptoms	Mild Symptoms	Moderate Symptoms	Severe Symptoms	Severe Symptoms
Conjunctival Staining[1]	Mild to Moderate	Moderate	Marked	Scarring
Corneal Staining[1]		Mild punctate	Marked punctate central	Severe punctate erosions
Tear Film[2]		Visual signs	Visual signs	Visual signs
Other[2]			Filamentary keratitis	Filamentary keratitis
Example Staining				
Example Artificial Tear Use	Less than 2X per day	Several times per day	Several times per day	Several times per day
Tear Film Breakup Time[2] (sec)	Variable	≤ 10	≤ 5	Immediate
Schirmer Score[2] (mm/5 min)	Variable	≤ 10	≤ 5	≤ 2

[1]Behrens et al. *Cornea.* 2006;
[2] Management and Therapy Subcommittee. *Ocul Surf.* 2007.

General Treatment Guidelines

Severity Level	1	2	3	4
Symptoms	Mild to moderate	Moderate to severe	Severe	Severe
Conjunctival Signs	Mild to moderate	Staining	Staining	Scarring
Corneal Staining		Mild punctate staining	Marked punctate staining; central staining; filamentary keratitis	Severe staining; corneal erosions
Other Signs		Tear film; vision (blurring)		

Treatment Options

1	2	3	4
• Patient education • Environmental modification • Preserved tears • Control allergy	• Unpreserved tears • Gels, ointments • Topical prescription therapies • Secretagogues • Nutritional support	• Oral tetracyclines • Punctal plugs (once inflammation is controlled)	• Systemic anti-inflammatory therapy • Oral cyclosporine • Acetylcysteine • Moisture goggles • Surgery (punctal cautery)
If no improvement, add level-2 treatments →	*If no improvement, add level -3 treatments* →	*If no improvement, add level-4 treatments* →	

Meibomian Gland Disease – Treatment Options
Lid hygiene; thermomassage; oral tetracyclines

Behrens et al. *Cornea.* 2006.

Role of AT's

- Osmolarity lowering
  - Refresh Optive, Blink Tears & TheraTears
- ABMD/corneal staining
  - FreshKote
- Lipid Deficient
  - Systane Balance, Soothe XP, Retaine MGD, Refresh Optive Advanced
- Aqueous deficient
  - Optive Gel/Refresh, Systane Ultra
- Severe
  - Systane/Genteal Gel or Ointment

Medical Therapies

- Restasis
- Xiidra
- Steroids
- NSAIDs
- Plugs
- Autologous Serum
- Compounding Biologics (Cyclosporin, Tacrolimus)
- ProKera
- Fish Oil (EPA/DHA, Ester v. TG, GLA/ALA Importance)
- Krill Oil
- Flaxseed Oil
- Vitamin C
- Scleral Contact Lenses
- TrueTear

Restasis

- Cyclosporine is an immunosuppressive agent when administered systemically.
- In patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca, cyclosporine emulsion is thought to act as a partial immunomodulator. The exact mechanism of action is not known.
- Approved in 2003.
- 14 years of Clinical Data.

Xiidra

- Lifitegrast is a small-molecule integrin antagonist that binds to the integrin lymphocyte function-associated antigen-1 (LFA-1), a cell surface protein found on leukocytes, and blocks the interaction of LFA-1 with its cognate ligand intercellular adhesion molecule-1 (ICAM-1). LFA-1/ICAM-1 interaction can contribute to the formation of an immunological synapse resulting in T-cell activation and migration to target tissues.
- Original R&D Lead: Dr Michael Stern
- Approved August 29, 2016.

Xiidra: Cont'd

- On Label recommendation is for the treatment of signs and symptoms of dry eye disease.
- Considered a new class of anti-inflammatory.
- Dosed 2x/daily and preservative free.
- Pivotal data suggests confidence intervals for improvement in symptoms in at 6 and 12 weeks, with some noticing improvement at week 2.
- Side effects similar to Restasis with the addition of dysgeusia (taste alteration).
  - **Pearls:** Dose in the office. After instillation, instruct to lean head forward to minimize oropharyngeal penetrance.
  - **Experience:** My explanation for the taste is bitter coffee left on the burner too long throughout the day.

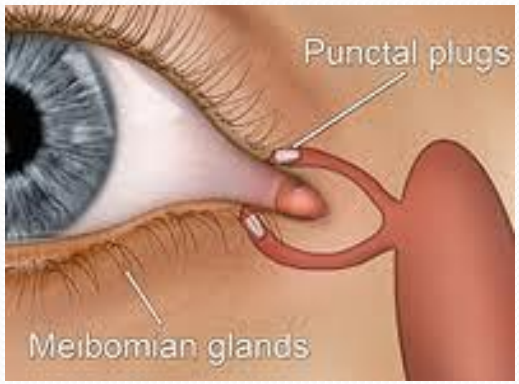
Topical Steroids and NSAIDs

- Lotemax Gel/Suspension/Ointment
- Prednisolone Acetate 1%/.12%
- Fluorometholone Acetate
- Loteprednol
- Prolensa
- Ilevro
- Ketorolac
- Bromsite (not commercially available yet)

All Off-label use, but we all know extremely effective when paired simultaneously with Restasis and now Xiidra

Plugs, Goggles, and Masks

- Plugs
  - Silicone Permanent
  - Collagen 3 to 180 days



- Moisture Goggles
  - Customizable

- Masks
  - Bruder
  - Rhein Medical

Compounding Biologics

- Autologous Serum
  - 20 to 50% (I prefer 20%)
  - Work closely with compounder to tailor the product to your specifications
- Ciclosporin-A
  - .05 to 2%
  - Solution vs. Emulsion (Corn or Olive Oil)
- Tacrolimus
  - .03%
  - Olive Oil

****Ciclosporin and Tacrolimus both require baseline & quarterly liver panels****

Nutritional Supplementation

- Vitamin C (2 g)
- Fish Oil = Omega 3
  - EPA/DHA
  - Ester v. TG
  - GLA (Black Currant Seed Oil)
- Krill Oil = Omega 3
  - Questionable efficiency due to increased endogenous digestive absorption. Ecologic food chain dilemma too.
- Flaxseed Oil = ALA
  - Must be crushed to increase bioavailability

The Importance of GLA

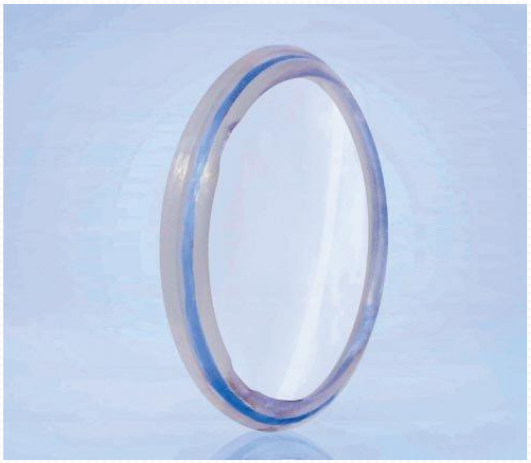
- GLA: more compelling array of evidence (vs. Fish oil – with fewer DE studies, often small doses in non-representative populations, e.g. Northern India, Iran)
- GLA has specificity for DE that fish oil omegas lack.
- Combining GLA + modest level EPA from fish oil, other nutrients / cofactors. GLA + EPA has complimentary effect on inflammation
- HydroEye: Commercially available DTC or in office from a Texas based company (ScienceBased Health)

7 Controlled Clinical Trials

- Aqueous-deficient (Barabino S et al. Cornea 22: 97–101, 2003.)
- PRK (Macri A et al. Graefes Arch Clin Exp Ophthalmol 241:561-6, 2003.)
- Sjögren's (Aragona P, et al. Ophthalmol Vis Sci 46:4474-9, 2005.)
- Contact lens (Kokke KH et al. Contact Lens Ant. Eye 31:141-6, 2008.)
- MGD (Pinna et al. Cornea 26:260-264, 2007.)
- Mild-moderate DE (Brignole-Baudouin et al. Acta Ophthalmologica 89:e591-7, 2007.)
- Post-menopausal women (***HydroEye***) (Sheppard JD, Pflugfelder SC, et al. Cornea 32 :1297-1304, 2013.)

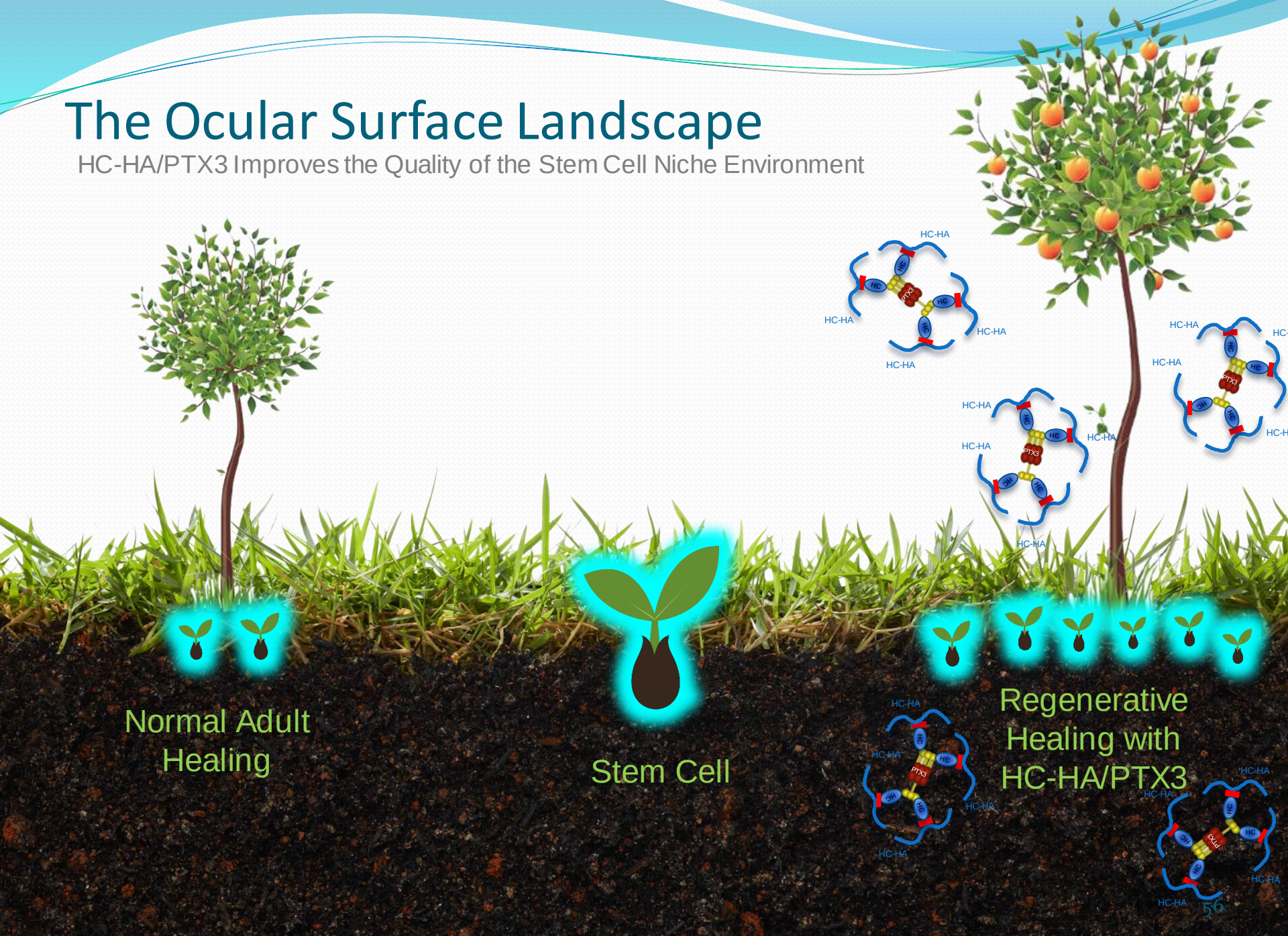
Amniotic Membranes

- Fetal Wound Healing
- Rapid uptake of nutrients and mobilization of stem cells.
- Similar to therapeutics, earlier initiation of membrane allows for better response.
- Cautionary Note
  - Wet cryopreserved = Wound Healing
  - Dry cryopreserved = Wound Coverage



The Ocular Surface Landscape

HC-HA/PTX3 Improves the Quality of the Stem Cell Niche Environment



Medical Devices

- Scleral Contact Lenses
- PROSE

- TrueTear (Allergan/Oculeve)
  - Neurostimulator
  - Think DBS (Deep Brain Stimulation)
  - Promising Device for: Tear & Meibum Production

New Delivery Platforms

- Nanotechnology
- Micronized Particles
- Therapeutic infused punctal plugs
- Therapeutic infused contact lens
- Sustained Release Injectables
- Sustained Release Rings
- Collimated Spray Device Cartridges

Seasonal/Perennial Allergies: A Family Affair

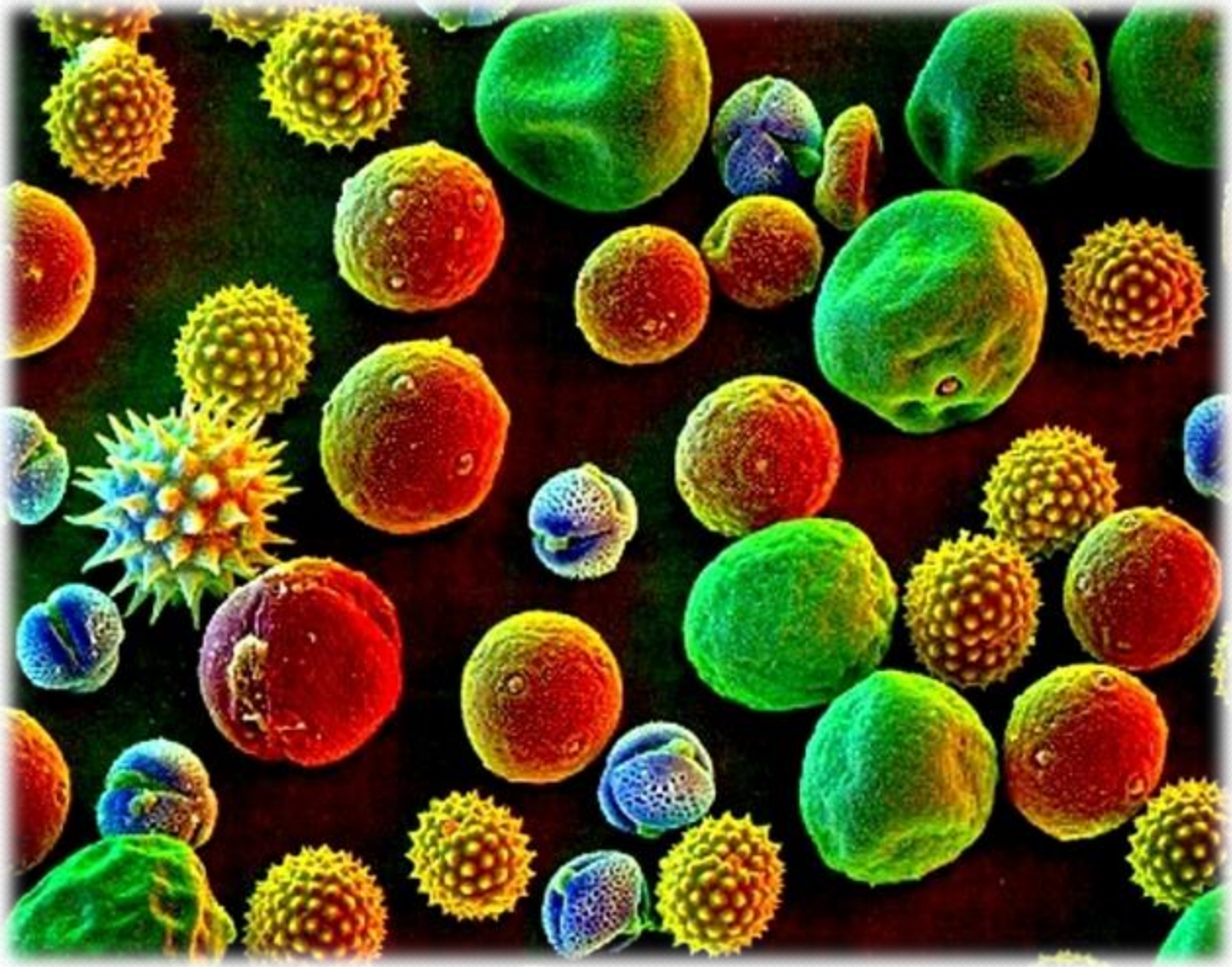
Figure 1. Dr. Cooper's 4-year-old daughter Hannah. She suffers from severe seasonal allergies.

Pediatric Pearl:
Magic Beans and Potions

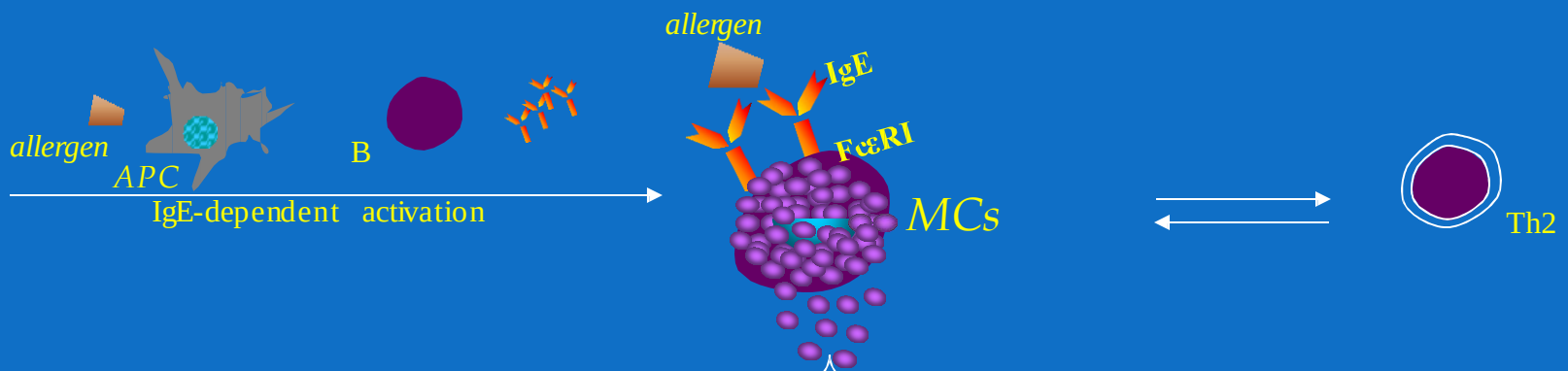
Medication, Drop, or Pill =
Non-adherence

Symptoms: The Top 5

- Itching/Pruritis
- Redness
- Chemosis
- Watering
- Runny nose



Allergic Pathway

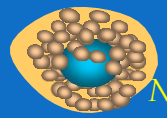


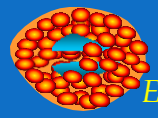
Early phase response
↑Ca^{2+} and degranulation

Histamine, tryptase, chymase, TNFα TGFβ1, NGF

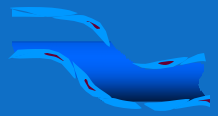
Late phase response
PKT down-stream (de novo synthesis)

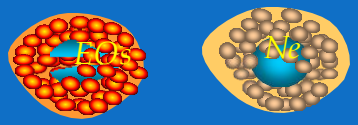
Leukotrienes, tromboxanes, IL6, IL8, IL5, IL10, TNFα, TGFβ1, NGF VEGF





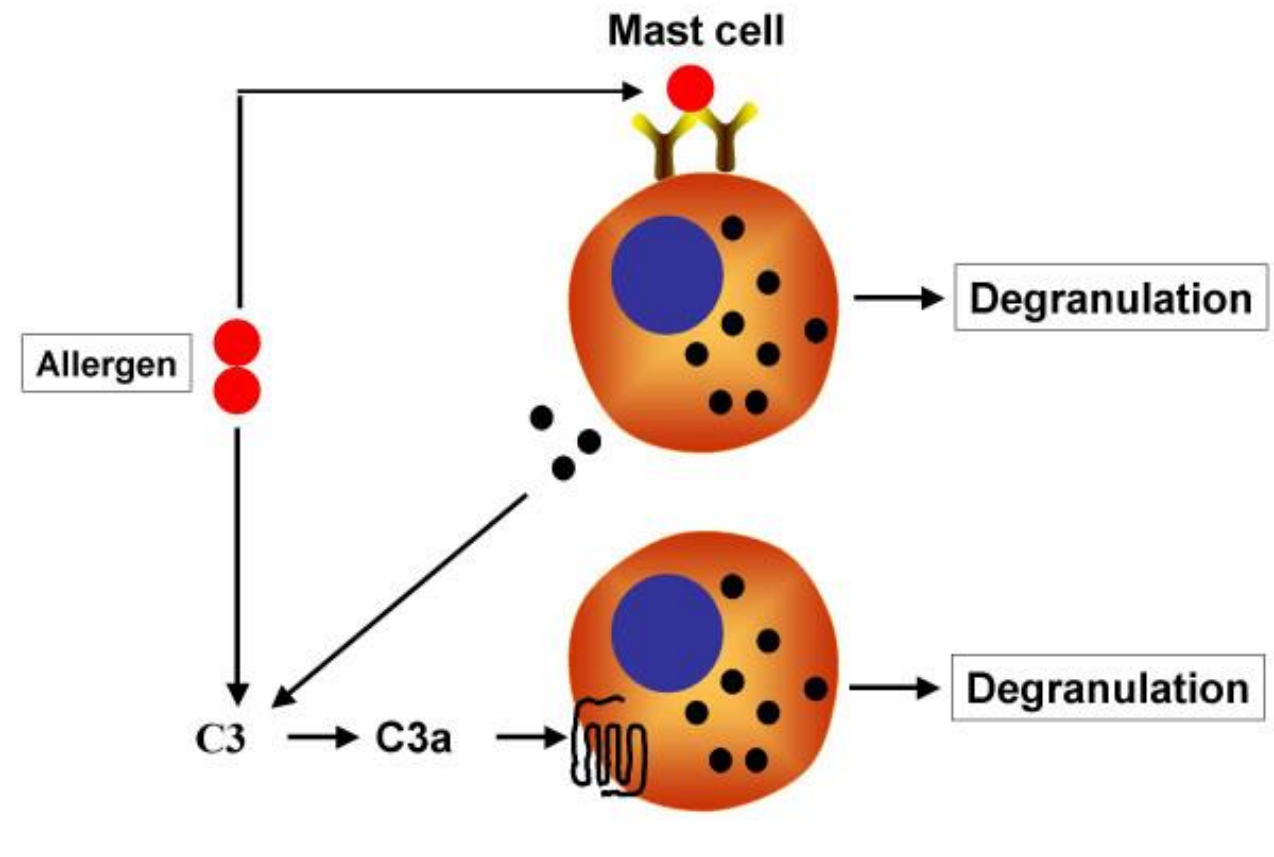
Chronic Inflammation and Tissue remodeling ocular surface damage





Simplified Allergy Model

(IgE-mediated hypersensitivity)



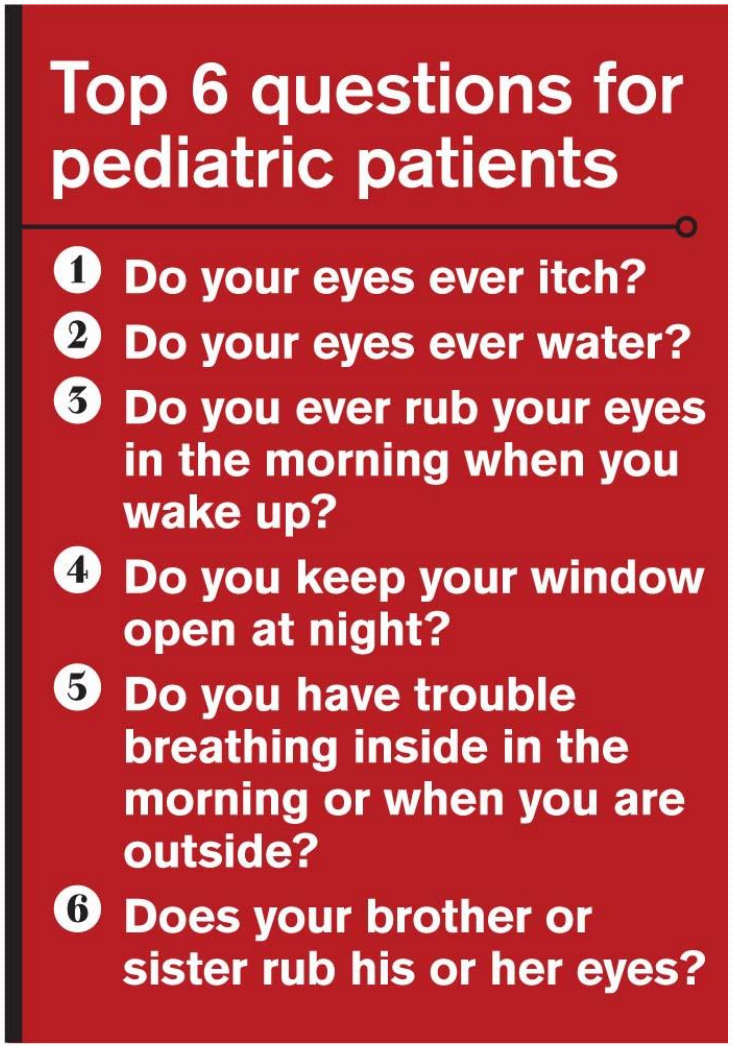
Back to Hannah….

Figure 2. Papillary reactionin 4-year-old child suffering from seasonal allergies.

Signs

- Sneezing
- Thin watery discharge
- No pre-auricular nodes
- No corneal involvement
- Hyperemia
- Papillary Reaction

Questions: For Kids and Adults



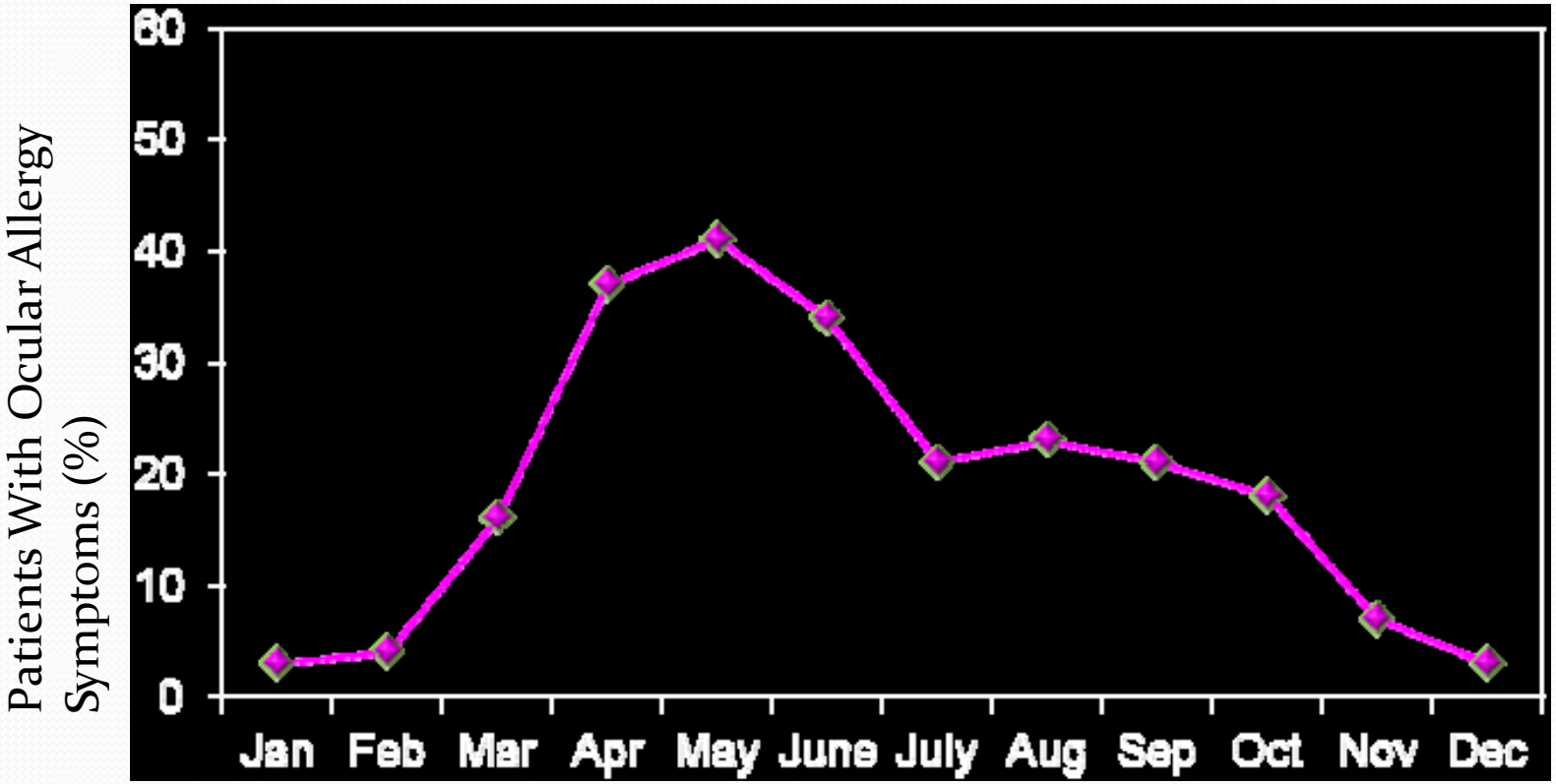
Prevalence of Allergic Conjunctivitis

- Increasing incidence over the last 40 years
- Over 20% of the general population are affected by allergic
- conjunctivitis
- In a study of 5000 children with allergies, 32% of children
- had only ocular symptoms
- Of 509 patients studied with “hay fever,” approximately

93% had conjunctivitis symptoms

  - Ocular symptoms predominated in 22% of patients, nasal symptoms in 25%, and both in 53%
- Ocular symptoms were mild in 25%, moderate in 53%, and severe in 22%

Ocular Allergy Symptoms by Month of Year (Findings from NHANES III Survey)



Molecular Vision 2011; 17:47-52 <http://www.molvis.org/molvis/v17/a7>

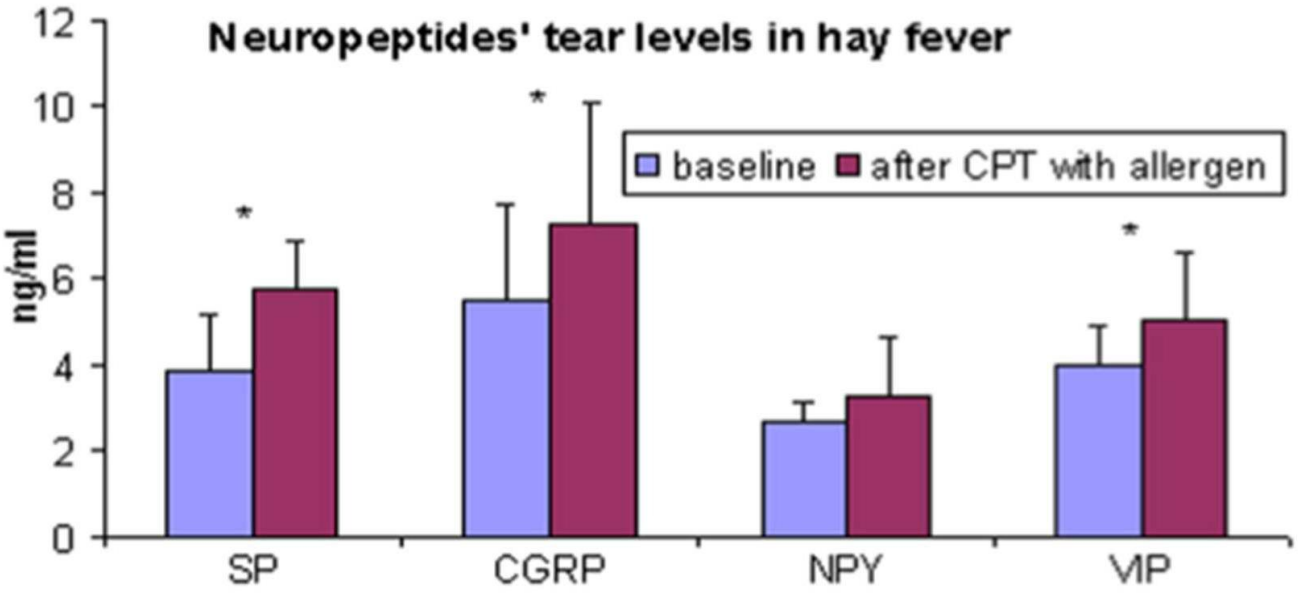


Figure 2. In allergic patients SP, CGRP, and VIP but not NPY tear levels significantly increase after a positive CPT.

Table 1 Treatment with preservative-free cromolyn sodium 4%-chlorpheniramine maleate 0.2% eye drops inhibited the local release of substance P, calcitonine gene-related peptide, neuropeptide Y, and vasoactive intestinal peptide after conjunctival provocation test

	Baseline (visit 1)			After treatment with cromolyn sodium (visit 2)		
Neuropeptides	Before CPT	After CPT	*P* value	Before CPT	After CPT	*P* value
Substance P (ng/ml)	3.2 ± 2	5.1 ± 2.3	0.03	3.2 ± 2.3	3.7 ± 1.4	NSS
CGRP (ng/ml)	3.9 ± 1.5	6.2 ± 2.4	0.04	5 ± 1.5	4.9 ± 2.5	NSS
NPY (ng/ml)	2.8 ± 0.4	3.7 ± 1.5	NSS	3.2 ± 1.2	4 ± 1	NSS
VIP (ng/ml)	3.6 ± 0.6	5.2 ± 1.7	0.03	3.7 ± 0.6	4.2 ± 0.8	NSS

CGRP, calcitonine gene-related peptide; CPT, conjunctival provocation test; NPY, neuropeptide Y; NSS, non statistically significant; VIP, vasoactive intestinal peptide.

Vernal Conjunctivitis

Features

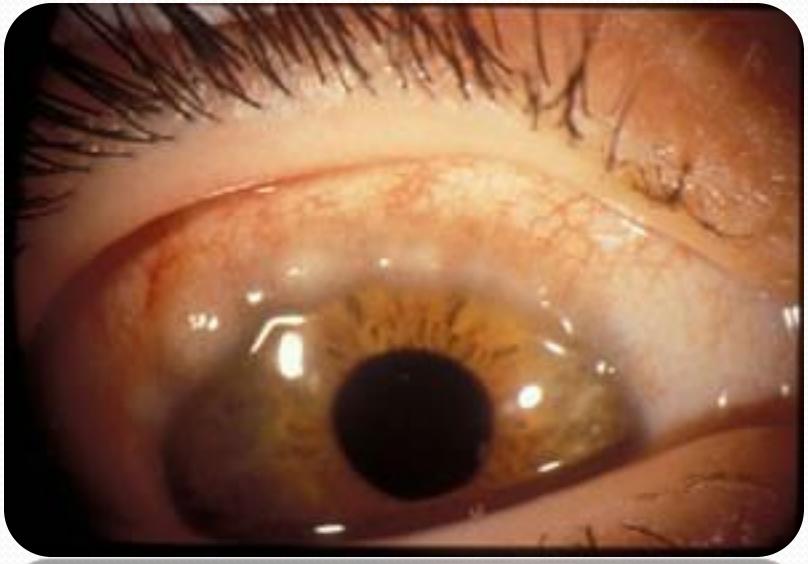
- Young age (mostly boys)
- Seasonal/Perennial
- Perilimbal pigmentation
- Papillary reaction
- Horner Trantas dots
- Ropy discharge
- Intense itching
- Ptosis from lid swelling
- Runny nose

Palpebral

- Giant papillae
- Shield ulcers

Limbal

- Limbitis (*Trantas dots*)



Substance P: Another Linkage

Investigative Ophthalmology & Visual Science, September 1997, Vol. 38, No. 10

Increased Plasma Levels of Substance P in Vernal Keratoconjunctivitis

Alessandro Lambiase,† Stefano Bonini,†‡ Alessandra Micera,* Paola Tirassa,* Laura Magrini,§ Sergio Bonini,§ and Luigi Aloe**

.001; Table 1). Moreover, NGF levels were dramatically ıcreased in the plasma of VKC patients (11,037 ± 10,641 g/ml; median, 130 pg/ml; $P < 0.001$) compared with evels in the plasma of control subjects (47.5 ± 8.5 pg/ ıl; median, 42.5 pg/ml).

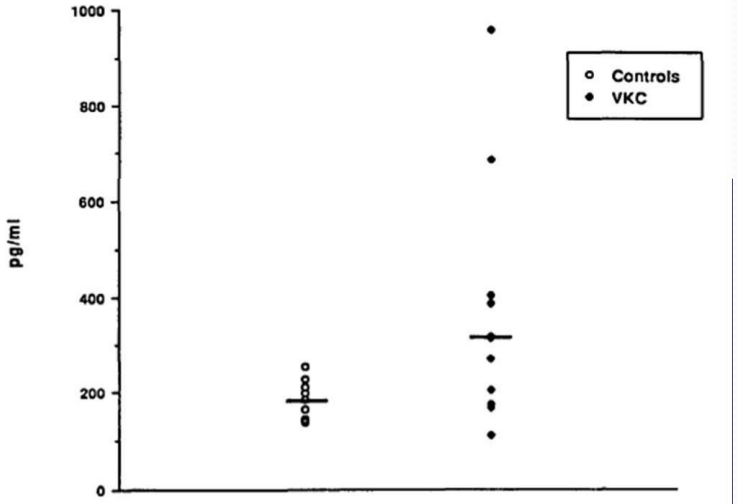
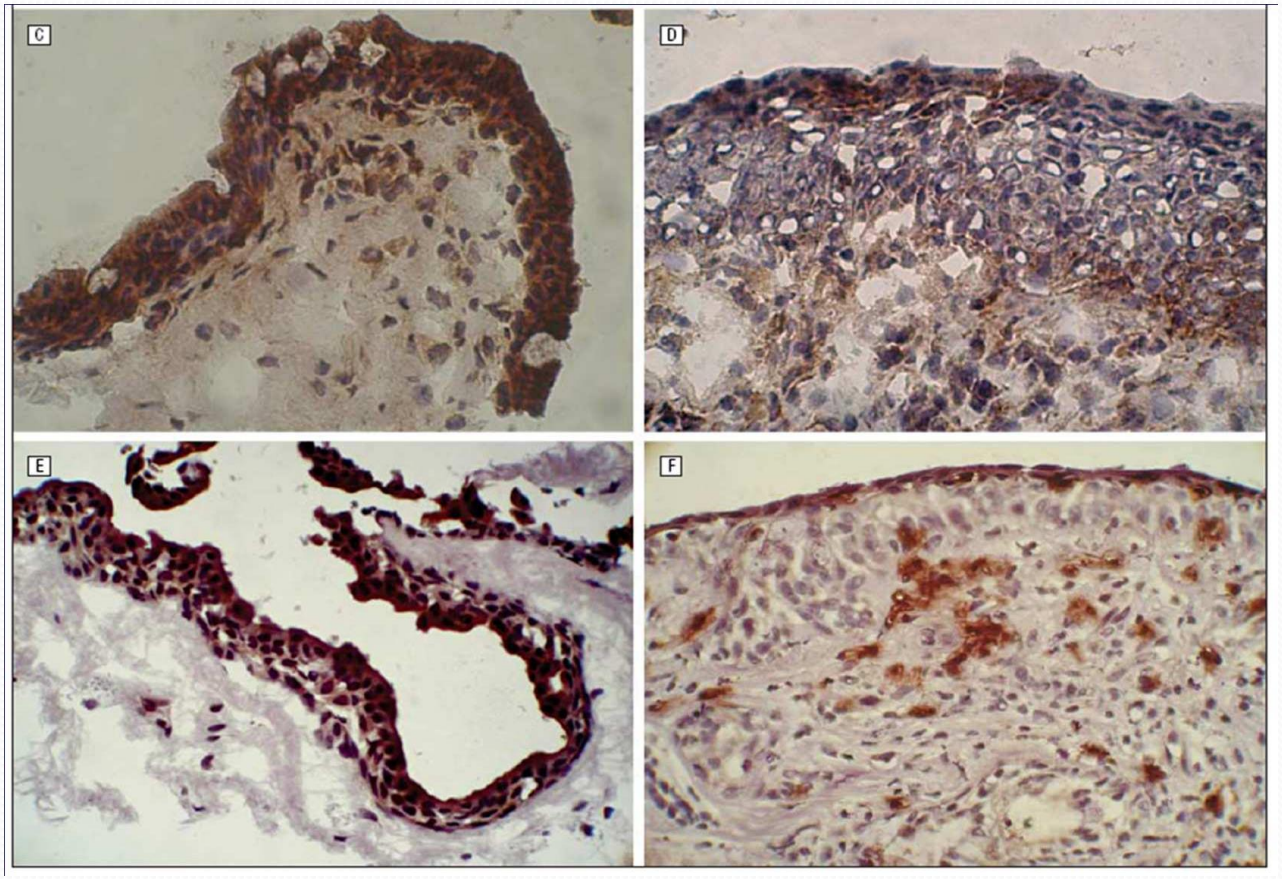


FIGURE 1. Substance P (SP) plasma concentration in vernal keratoconjunctivitis (VKC) patients and control subjects. The horizontal bars represent the medians of the values. Readings in the two groups differ significantly ($P < 0.001$).

Altered Expression of Neurotransmitter Receptors and Neuromediators in Vernal Keratoconjunctivitis

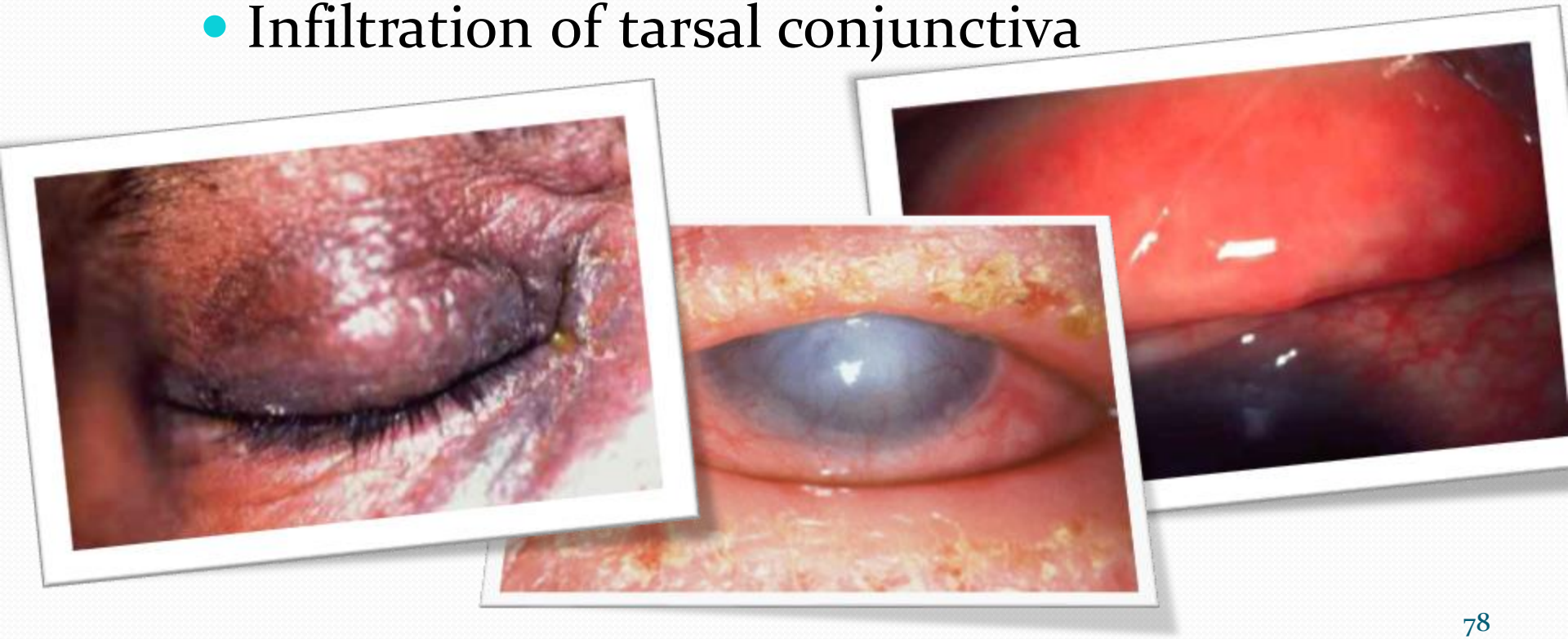
Laura Motterle, MD; Yolanda Diebold, PhD; Amalia Enríquez de Salamanca, PhD; Victoria Saez, BS; Carmen García-Vázquez, BS; Michael E. Stern, PhD; Margarita Calonge, MD; Andrea Leonardi, MD



Atopic Conjunctivitis

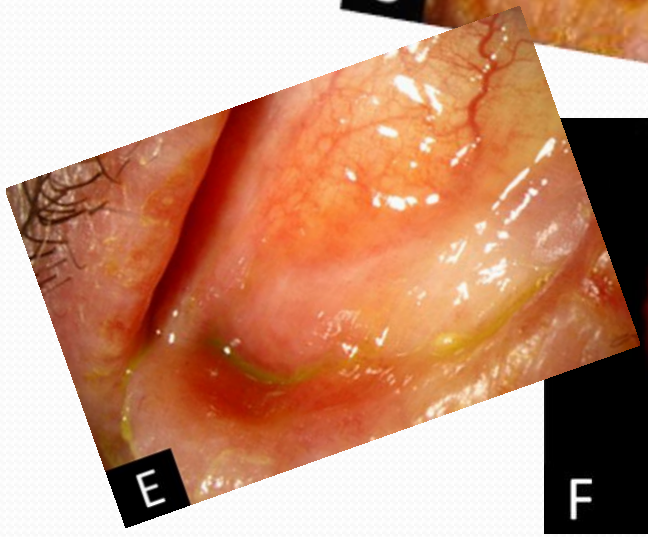
Features

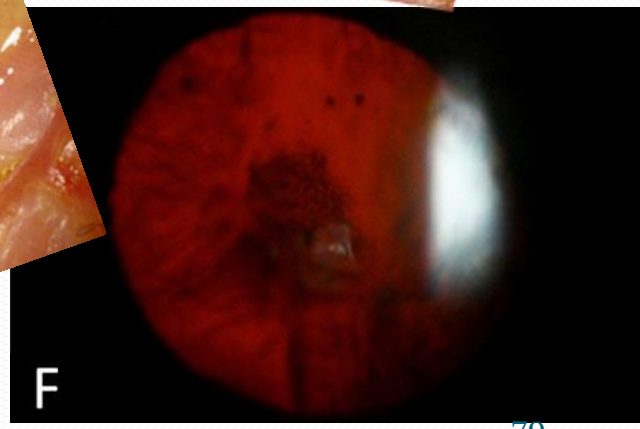
- Males (Teens to 50's) / No Seasonal Component
- Atopy Triad (Allergy, Eczema, Asthma)
- Red, thickened, macerated lids
- Infiltration of tarsal conjunctiva



Complications

- Persistent epithelial defects
- Corneal Scarring
- Superinfection
- Corneal neovascularization
- Pannus
- Cicatrization
- Keratoconus
- Cataract (ASC/PSC)
- Symblepharon
- Blepharitis
- Diathesis

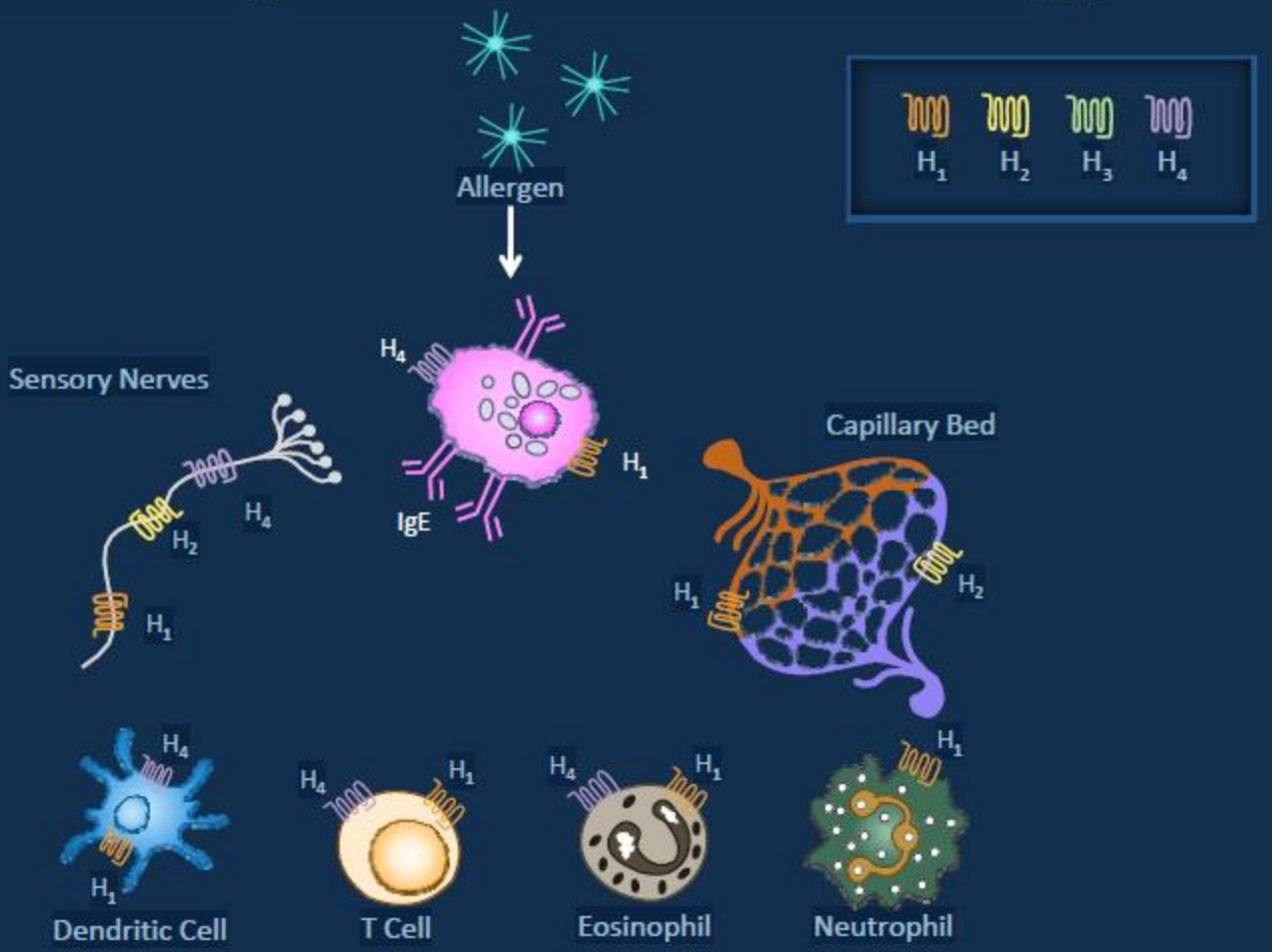




Diagnostic Allergy Testing

- Doctor's Rx Allergy Formula

The Role and Location of Histamine in Tissues Implicated in Ocular Allergy



Abelson and McLaughlin. *Rev Ophthalmol*. 2011; Leonardi et al. *Allergy*. In press; Bielory and Ghafoor. *Curr Opin Allergy Clin Immunol*. 2005.

Treatment Methods

Straightforward/Early

- Antihistamine/Mast Cell Stabilizers
  - Pazeo, Bepreve, Lastacaft, Pataday, Epinastine, Zaditor
- Oral and Topical Antihistamine
  - Azelastine, Loratidine, Zyrtec, Xyzal, Allegra
- Mast Cell Stabilizers
  - Cromolyn Sodium 4%
- Steroids
- Cold Compresses/Preservative Free Tears

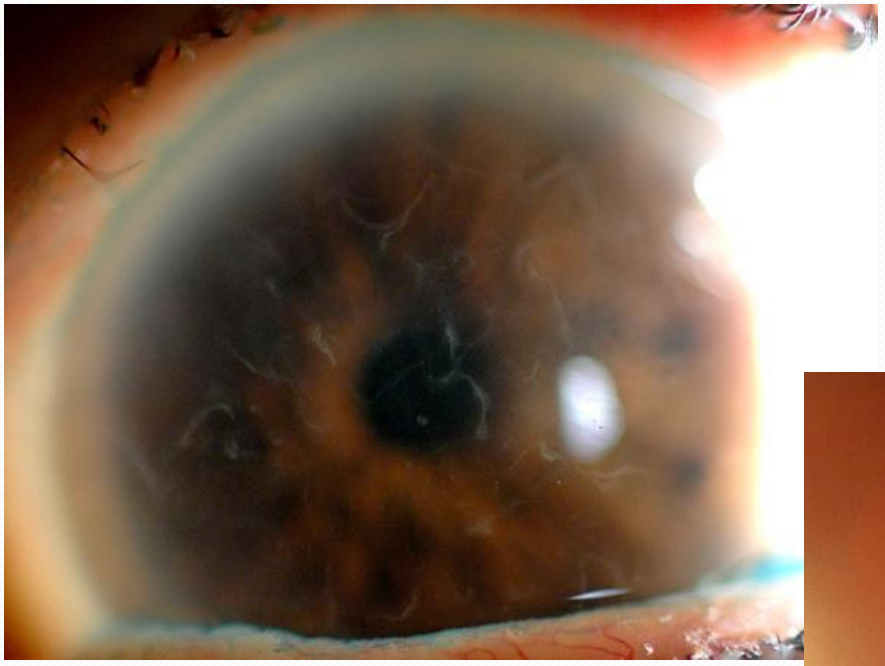
Treatment Methods

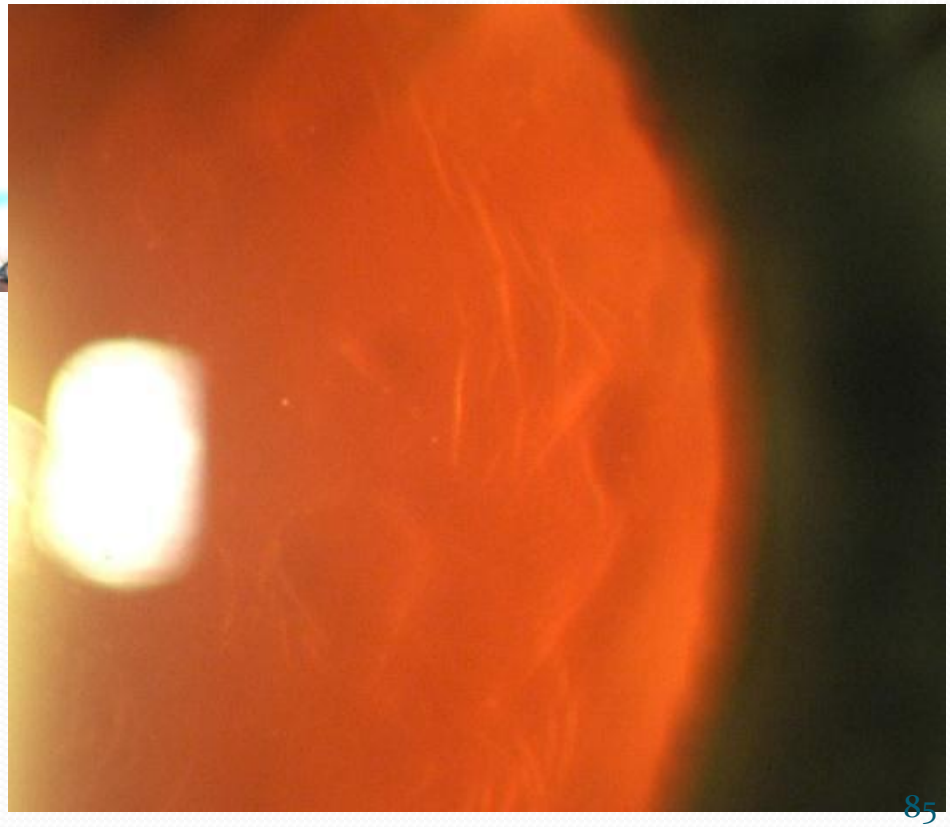
Advanced Stage (Vernal and Atopic)

- Cyclosporine A 0.05% eye drops (V&A)
- Tacrolimus 0.03% ointment to the eyelid skin (A)
- Topical corticosteroid 4-6x/day (A)
  - Shield Ulcers (V)
- ***Consultation with allergist and/or dermatologist***
- Oral cyclosporine, tacrolimus, or corticosteroids (A)
- Boston Keratoprosthesis– if visual loss from corneal opacification has occurred (A)

Recurrent Corneal Erosion (Syndrome)

- Chronic relapsing disease of corneal epithelium
- Characterized by disturbance of epithelial basement membrane
- Defective adhesions
- Recurrent breakdown of corneal epithelium
- Redness, photophobia, tearing
- Usually at night or upon awakening
- May be related to REM during sleep cycle





History

- First reported in 1872
  - Hansen
    - "Intermittent neuralgic vesicular keratitis"
    - Antecedent trauma
- Szili (1900)
  - "epithelial irregularities and gray dots"
- Stood (1900)
  - "trauma to corneal epithelium and anterior stroma → inability of new epithelium to form normal attachments to injured anterior Bowman's layer."
- Vogt (1921)
  - "fine white dots on Bowman's layer; fluorescein staining lines; irregular epithelial surface with localized edema."

Epidemiology

- Case Series; Brown, BJO 60:84-96,1976
  - Age 24-73
  - Highest incidence in 3rd and 4th decade (Avg: 42.5 yo)
  - Initial abrasion to 1st recurrence: 2days – 16 yrs
  - Dominant inheritance in 3%
  - 10% of cases are bilateral

Most Common Symptoms & Frustrations

- Pain
- Watering
- Blurred Vision

Management can be frustrating for both patient and doctor

- Patient discouraged because of recurrent pain and decreased vision
- Doctor disheartened by inability to cure disease

Etiology/Pathogenesis

Primary

- Epithelial basement membrane dystrophy
  - Map-dot-finger
- Dystrophies involving Bowman's layer
  - Reis-Bucklers
  - Thiel-Behnke
- Stromal dystrophy
  - Lattice
  - Macular
  - Granular

Secondary

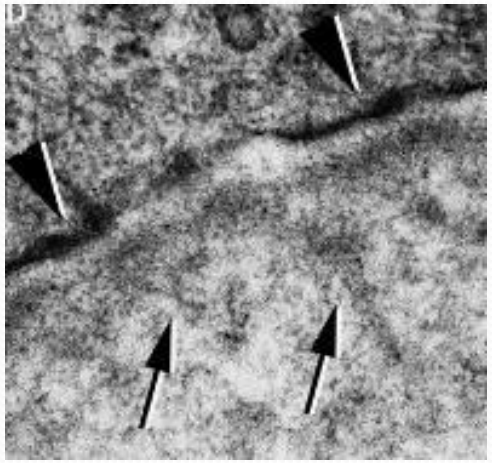
- Degeneration
- Trauma
- Post Refractive Surgery

RCE Snackable Bits

- Incidence of RCE 1:150 cases following a traumatic abrasion
- Majority – 87% (one study) occur within the lower half of the cornea irrespective to the etiology
  - In close proximity to Hudson-Stahli line
- Tiredness, menopause, menstruation, and alcohol were recognized as aggravating factors
- EBMD cases who suffer trauma are more likely to suffer from RCE

Anatomy Rundown

- Epithelial cells rest on the basement membrane - 128nm
- **Lamina Lucida**
  - made of glycoprotein laminin secreted by overlying epi
- **Lamina Densa**
  - made of Type IV collagen secreted by overlying epi
- **Lamina Reticularis**
  - made of fibronectin secreted by underlying stroma
- Normal adherence to BM maintained by "adhesion complexes":
- Hemidesmosomes (arrowhead)
- Lamina lucida and densa
- Anchoring fibrils (arrows)
- Laminin
- Fibronectin
- Type IV and VII Collagen



Anatomy Dysregulation

- Reattachment of corneal epithelium following an abrasion appears faulty
- Variety of adhesion complex defects have been observed
  - Reduplication of BM
  - Loculation of connective tissues
  - Absence of BM and hemidesmosomes
- Corneal Epithelium
  - develops pale, swollen basal cells
  - pseudocystic collections of cellular and amorphous debris are found within the epi (due to aberrant BM)
- Leads to elevation of epi and accumulation of underlying debris and the further formation of abnormal BM
- Cycle self-perpetuates

- Epithelium separation is maximal at night due to superficial edema induced by hypotonicity of tears caused by lack of evaporation
- During lid closure, the surface tension of the tears will cause an adherence between the lids and corneal epithelium
- Opening the eyes quickly creates a shearing force, which is greater than the force of adherence of the affected epithelium which results in epithelial avulsion

How to Communicate RCE

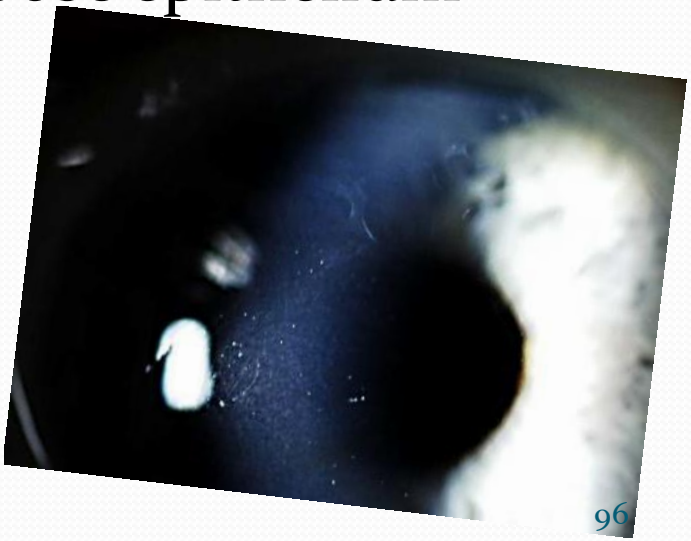
- Skin of the eye is not healing or bonding correctly
  - Primer and Paint
  - Crumb coat and Fondant

What To Say If "Things" Go South

- More often than not, these conversations occur after the 2nd or more commonly 3rd episode.
  - **Pearl**: Apologize without apologizing.
- Create an actionable plan
  - Allow for patient input
  - Explain customization
- Share latest technology
  - Motivate

Diagnosis

- Hx of previous trauma to involved eye
- SLE with indirect illumination
- Retroillumination after dilation
- Ragged greyish-staining area of epithelium
- Cellulose sponge test looking for loose epithelium
- "positive cellulose sponge test"
- Topography
- Anterior OCT Imaging



Treatment Options

Medical – (>95% successfully managed, 70% remaining symptom free x 1 yr, 40% 4 years)

- Promoting epithelial regeneration
- Patching (rare), bandage contact lenses
- Antibiotics, cycloplegics, hyperosmotics, corticosteroid, immunomodulation
- Oral tetracyclines and Vitamin C
- Mechanical

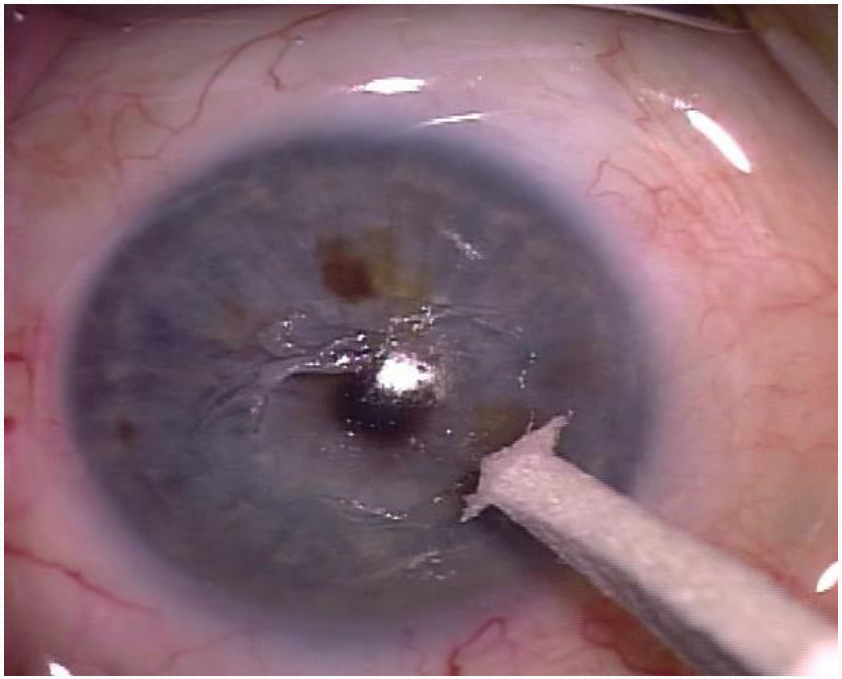
When medical management is not successful

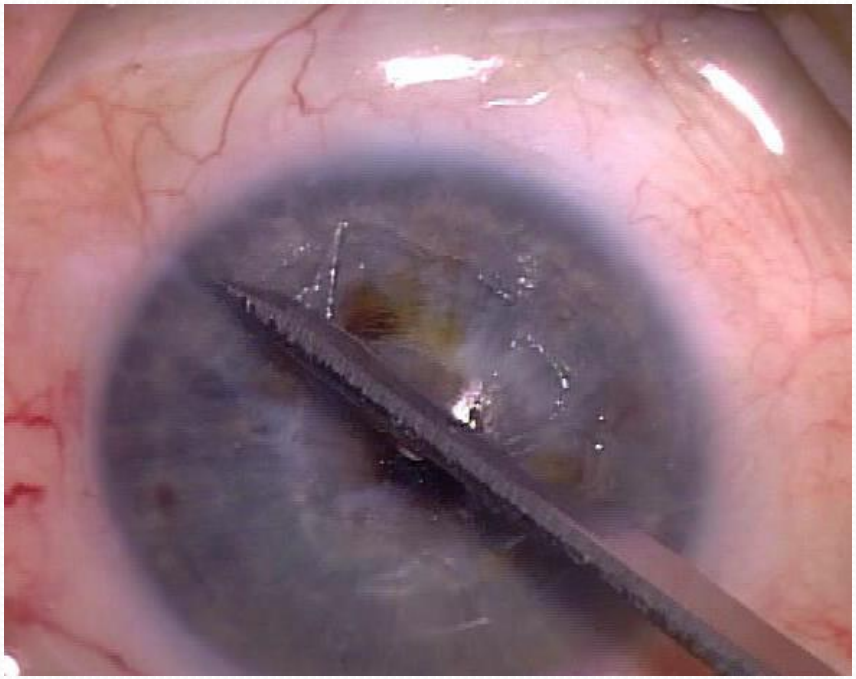
- Debridement + Amniotic Membrane
- Anterior Stromal Puncture (ASP)
- Surgical
- Phototherapeutic keratectomy (PTK)
- Diamond burr superficial keratectomy
- Nd:YAG
- Alcohol Delamination

Autologous Serum

- When applied on RCE
- Extra supply for necessary glucose, proteins and calcium for the epithelium to migrate rapidly
- Speeding up first phase of wound healing
- Vitamin A and fibronectin also help speed this up
- Affects final phases of wound healing by supplying necessary extracellular matrix components
- Supplies growth factors that activates keratocytes to produce extracellular matrix components

Debridement Methods

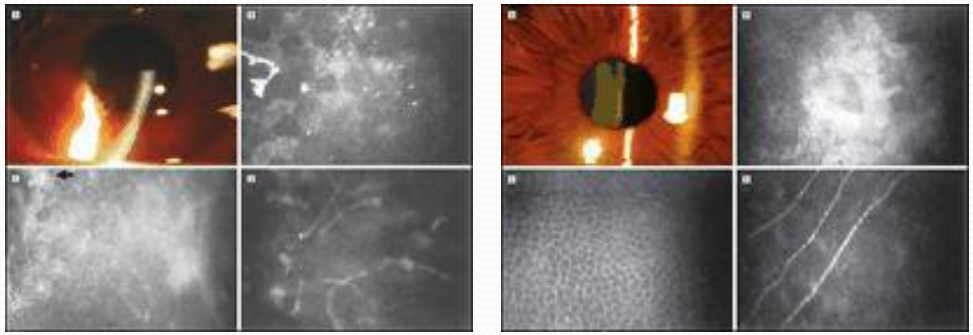




Substance P Case Study

- 32 yr old female patient with 26 RCE episodes
- Eye drops 4x/d combining 250 µg/mL of substance P–derived peptide with 1 µg/mL of insulin-like growth factor I
- Resolution of defect noted in 11 days
- Tx D/C after 2 mo's
- 11 months no recurrence

**More studies needed

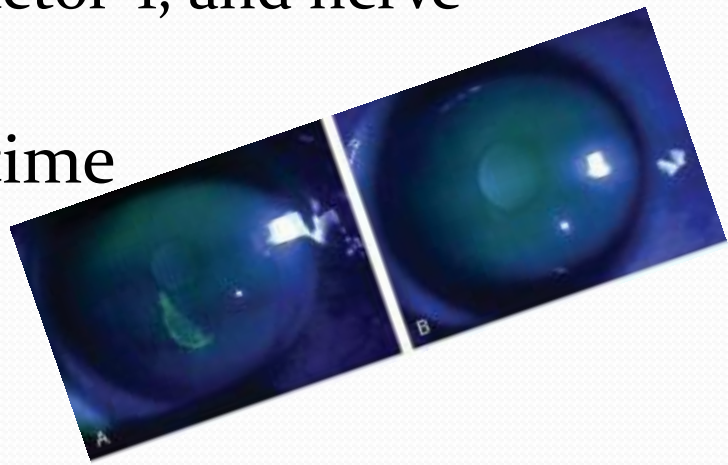


Before After

Benitez-Del-Castillo. *Treatment of Recurrent Corneal Erosion With Substance P–Derived Peptide and Insulin-like Growth Factor I. Arch Ophthalmol* 2005

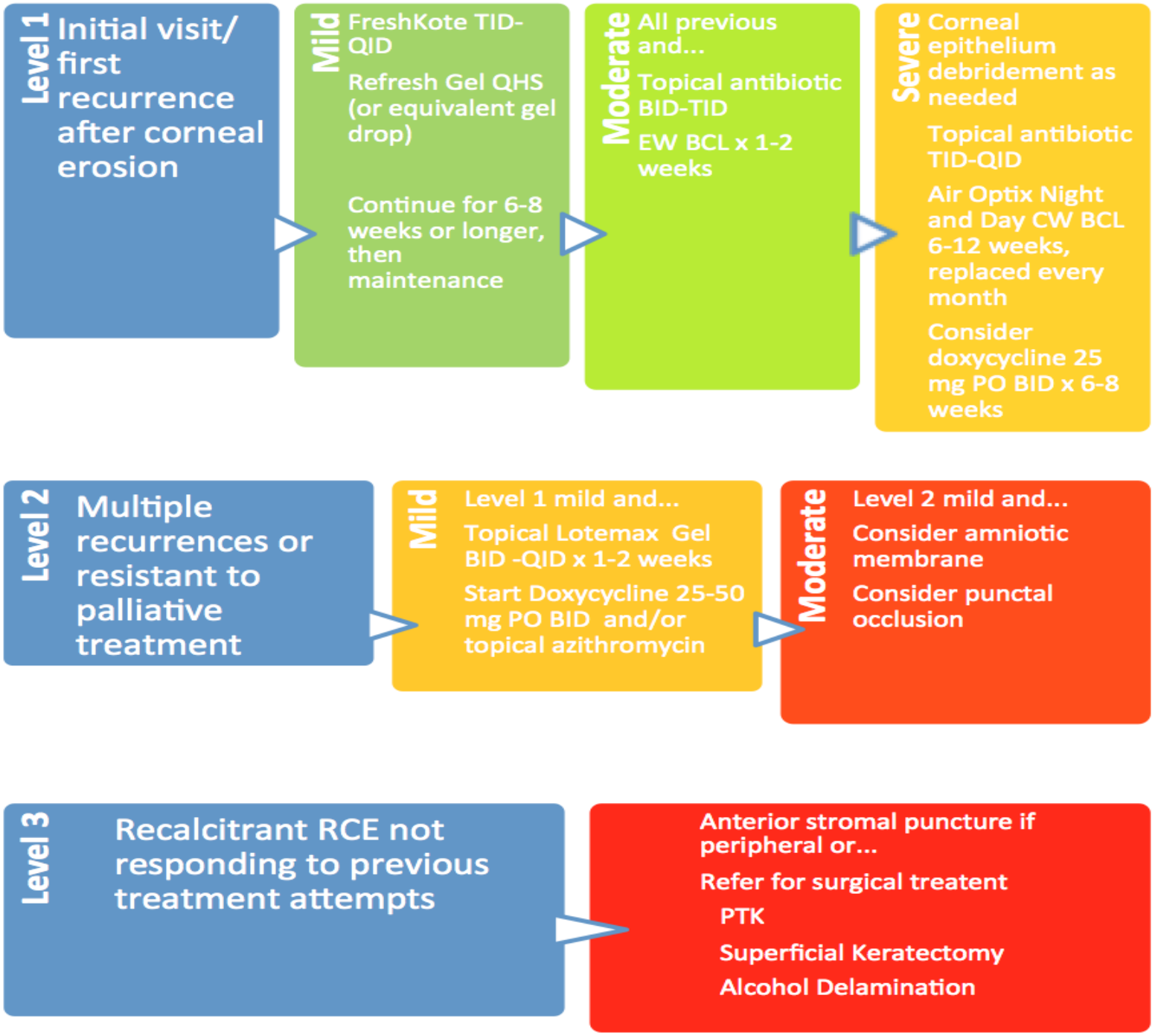
Umblical Cord Serum

- Compared to AS, UC serum
- Higher concentration of essential tear components
- Many growth factors
  - Epidermal Growth Factor, Vitamin A, and Transforming Growth Factor-b, and neurotropic factors, such as Substance P, insulin-like growth factor-1, and nerve growth factor
- 35 pts, f/u 14 mo, tx 4-6x/d entire time
- 83% success



Yoon K, Choi W, You I, Choi J. Application of Umbilical Cord Serum Eyedrops for Recurrent Corneal Erosions. Cornea. 2011;30:744-748.

Seeing Triple?

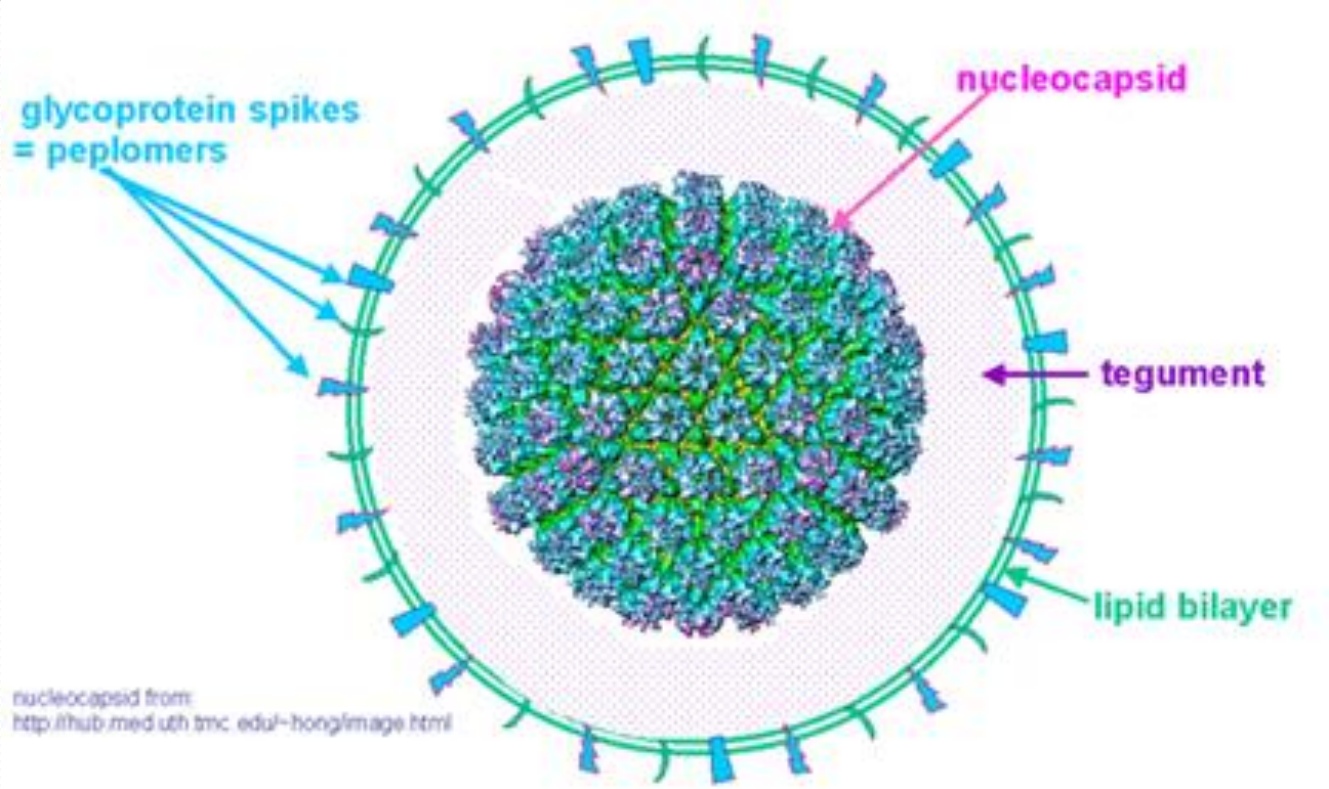

Level 1
Initial visit/ first recurrence after corneal erosion
Mild
FreshKote TID-QID
Refresh Gel QHS (or equivalent gel drop)
Continue for 6-8 weeks or longer, then maintenance
Moderate
All previous and...
Topical antibiotic BID-TID
EW BCL x 1-2 weeks
Severe
Corneal epithelium debridement as needed
Topical antibiotic TID-QID
Air Optix Night and Day CW BCL 6-12 weeks, replaced every month
Consider doxycycline 25 mg PO BID x 6-8 weeks
Level 2
Multiple recurrences or resistant to palliative treatment
Mild
Level 1 mild and...
Topical Lotemax Gel BID -QID x 1-2 weeks
Start Doxycycline 25-50 mg PO BID and/or topical azithromycin
Moderate
Level 2 mild and...
Consider amniotic membrane
Consider punctal occlusion
Level 3
Recalcitrant RCE not responding to previous treatment attempts
Anterior stromal puncture if peripheral or...
Refer for surgical treatent
PTK
Superficial Keratectomy
Alcohol Delamination

Herpesviridae

- Members of the herpesvirus family have been identified in more than 80 different animal species.
- Eight have been identified as human pathogens.
- Herpes viruses are a leading cause of human viral disease, second only to influenza and cold viruses.
- Herpes viruses infect most of the human population and persons living past middle age usually have antibodies to many of the human herpesviruses.

Herpesviridae Composition

- Comprises large, DNA-containing enveloped viruses



Infection and Location

Designation	Common Name	Subfamily	Associated Diseases
HHV-1	HSV-1	Alpha	Oral Herpes (cold sore), Genital Herpes
HHV-2	HSV-2	Alpha	Genital Herpes
HHV-3	VZV	Alpha	Chicken Pox, Shingles
HHV-4	EBV	Gamma	Mononucleosis, Lymphoma, Carcinoma
HHV-5	CMV	Beta	Mononucleosis, Retinitis, Transplant Rejection
HHV-6	HHV-6	Beta	Roseola infantum, Mononucleosis syndrome, Chronic fatigue syndrome, Multiple Sclerosis?
HHV-7	HHV-7	Beta	Roseola infantum?, Mononucleosis syndrome?
HHV-8	KSHV	Gamma	Kaposi's Sarcoma

Pump the Brakes: How Do You Break the News?

a) Rip it off like a band aid ala 40 Year Old Virgin?

b) Sympathize and drone on for 5-10 minutes?

c) Sympathize, state the facts, and deliver your Tx plan?

d) I don't want to tell them, let's delegate it the technician!

α herpesviruses

- Fast replicating
- Variable host range
- Typically destroy host cell (lysis)
- Latency established in sensory ganglia
- 90% Seropositive
- Initial infection is typically subclinical (6 mo – 6 yr)
  - Self limiting– Usually

Herpes Simplex virus-1 and 2 (HSV-1/HSV-2)
Varicella-Zoster virus (VZV

Herpes Simplex Virus

There are two types with very similar characteristics

- HSV-1 (HHV-1)
- HSV-2 (HHV-2)

The genome of HSV encodes a number of enzymes, including

- DNA-dependent DNA polymerase*
- Thymidine kinase*
- Ribonucleotide reductase
- Serine-protease
- Protease, RNase

*Since these are viral enzymes, they represent reasonable targets for drug therapy

Myth or Reality?

- HSV-1 and HSV-2 first infect cells of the mucoepithelia, or enter through wounds.

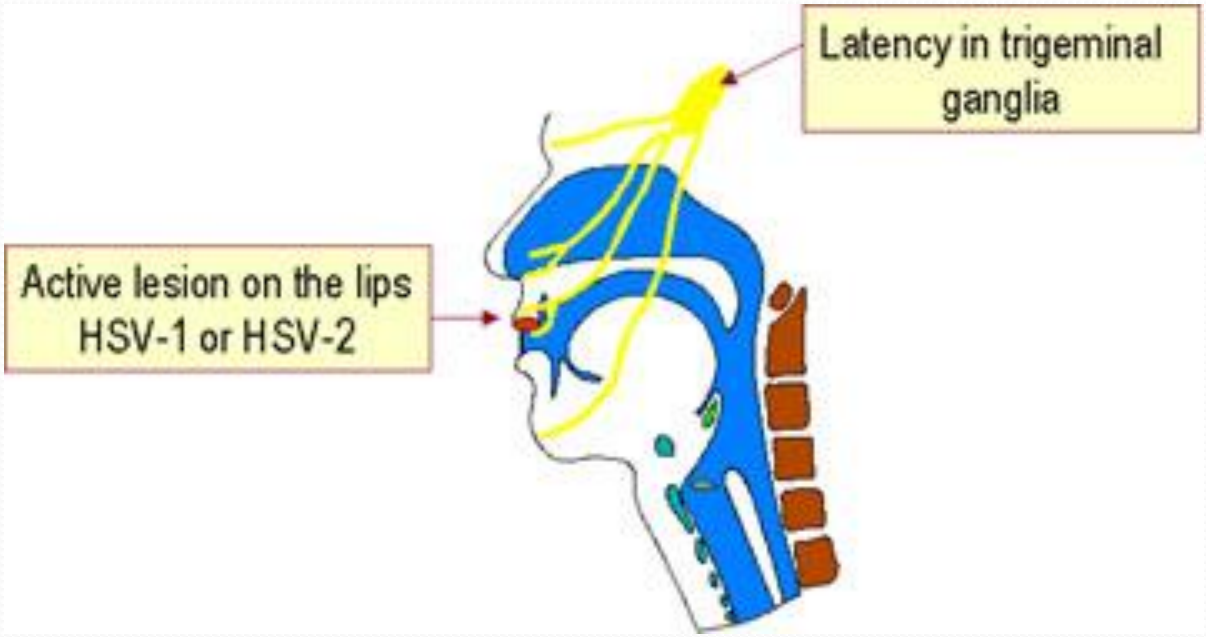
True!

- HSV-1 is only above the waist?
- HSV-2 is only below the waist?

False!

Latency

- HSV also infects neurons that innervate the epithelial tissue
- The virus travels along the neuron (retrograde transport)
- Oral mucosa -> Trigeminal ganglia
- Genital mucosa -> Sacral ganglia
- A latent infection is established in the nervous tissue, but not much is known of the mechanism of the Latency Activating Transcript (LAT)



Reactivation

Several agents may trigger recurrence

- Mental Stress or Fatigue
- Exposure to strong UV sunlight
- Fever
- Localized trauma (surgery)
- Hormonal changes (menstruation)
- Temperature changes
- Endogenous prostaglandins (ie. Latanoprost)

- The virus can travels back down the nerve axon and arrives at the mucosa that was initially infected

- Vesicles containing infectious virus are formed on the muscosa and the virus spreads

Recurrence by the Numbers

- United States: 20,000 new cases annually
  - 28,000 reactivations annually
- United States: Roughly 500,000 people with the disease

Recurrence Rates of ocular HSV (Liesegang et al. 1989)

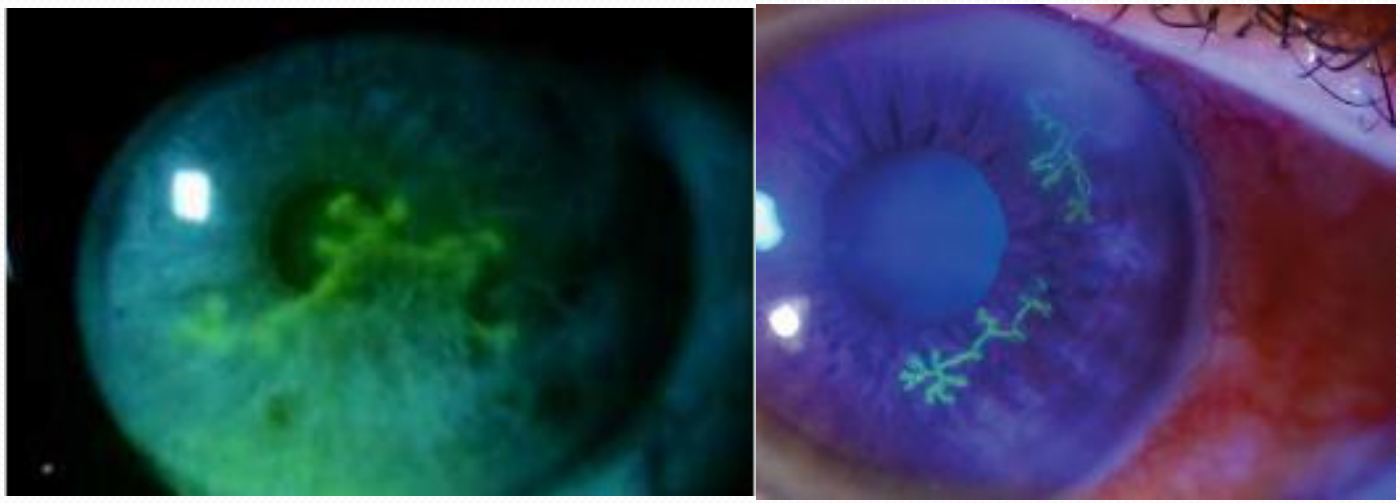
- 122 patients over 33 years
- Mean age of initial onset = 37.4 years
- 36% after 5 years
- 63% after 20 years
- After a second episode, 70-80% had another recurrence within 10 years

Ocular Manifestations of HSV

- Blepharitis
- Conjunctivitis
- Scleritis
- Keratitis
  - Epithelial
  - Stromal
  - Disciform
  - Endothelitis
- Iridocyclitis
- Retinitis

HSV Epithelial Keratitis

- Opaque cells form coarse punctate or stellate pattern
- Desquamation of center leaves linear branching ulcer
  - Fluorescein stains bed of ulcer
  - Lissamine Green/Rose Bengal stains virus-laden margin



HSV Epithelial Keratitis

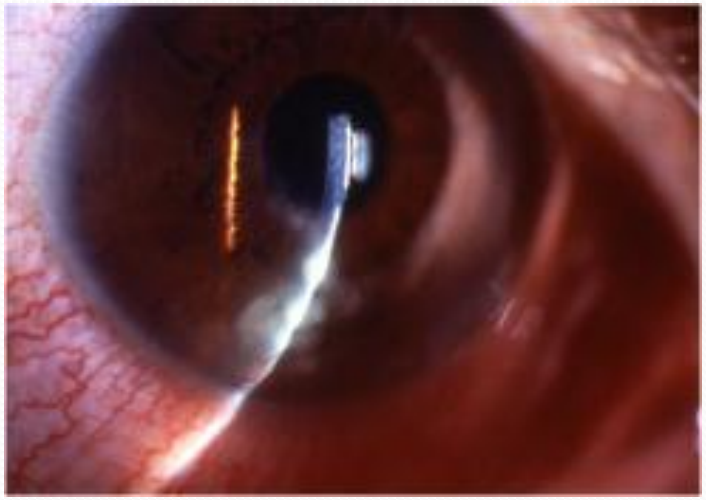
- Day 3-5 sub-epithelial anterior stromal infiltrates
- Occasional progression to geographic ulcer
  - If undertreated
- Healing phase –persisting pseudodendrites

Differential Dx/Masqueraders

- Herpes Zoster ophthalmicus
  - Typically Stellate and Peripheral
- Healing corneal abrasion
- Acanthamoeba keratitis
- Topical drop toxicity
- Pseudodendrite with SCL

**Pearl: If there is any semblance of a linear branch, stain with Lissamine/Rose Bengal!

Stromal Keratitis



Interstitial (Immune Stromal) Keratitis

Necrotizing Stromal Keratitis

Stromal Interstitial Keratitis

Etiology

- Immune reaction to retained viral antigen

Clinical Findings:

- Stromal haze / infiltration
- Intact epithelium
- Immune ring
- Keratic precipitates
- Previous stromal scars

Stromal Interstitial Keratitis

Clinical Course

- Often chronic and recurrent
- May occur weeks or months after IEK
- May occur w/o prior hx of IEK (~2%)

Persistent inflammation may lead to:

- Scarring
- Thinning
- Neovascularization
- Lipid deposition
- Loss / distortion of vision

Necrotizing Stromal Keratitis

Etiology

- Rare manifestation of HSV
- Viral invasion of stromal with severe inflammatory reaction
- Dense stromal infiltrate with overlying epithelial defect
- Thinning and perforation

Perfect moment to collaborate/refer to local Cornea or Uveitis Specialist

Stepping Back from the Abyss: HEDS I and II

- Landmark study that erased prevalent taboos and continues to define major aspects in the clinical care of herpetic eye disease

- With this being said, it was published 20+ years ago, and our understanding of ocular herpes infection and its management have progressed dramatically in that time

Guidance is nice, but not reality

- Assumes clear delineation between epithelial and stromal keratitis (Not always the case in practice!)

- Medications are on the market that were not included in the HEDS study. When do we prescribe them and not acyclovir and trifluridine?:
  - Valacyclovir (Valtrex®)
  - Ganciclovir (Zirgan®)
  - Famciclovir (Famvir ®)

- No guidance given for the use of topical vs. oral antivirals in forms of herpetic eye disease where equal efficacy was shown in HEDS…
- Well, they did happen to address it over the past few years!

Dendritic Epithelial Keratitis

1. Epithelial Keratitis

a. Dendritic

(Therapeutic dose of topical or oral antiviral agent)

Acyclovir (Zovirax®): 400 mg 3–5 times daily for 7–10 days **or**

Valacyclovir (Valtrex®): 500 mg twice daily for 7–10 days **or**

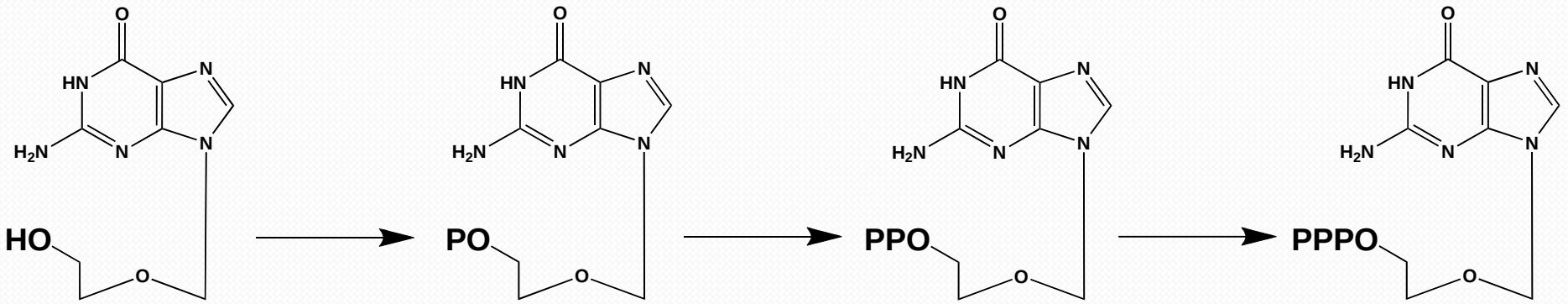
Famciclovir (Famvir®): 250 mg twice daily for 7–10 days **or**

Trifluridine ophthalmic solution 1% (Viroptic): instillation of 1 drop into affected eye(s) 9 times daily for 7 days; may decrease dose to 5 times daily after 7 days if ulcer is healed. Treatment should not extend beyond 21 days because of potential ocular toxicity.

or

Ganciclovir ophthalmic gel 0.15% (Zirgan®): instillation of 1 drop into affected eye(s) 5 times daily while awake until healing of corneal ulcer, followed by 1 drop 3 times a day for 7 days.

Acyclovir MOA



Acyclovir Triphosphate **Chain Terminator**

HSV Thymidine Kinase*

Monophospho Kinase

Diphospho Kinase

End Arounds in the Armor

Nucleoside Analogs

- Acyclovir (Zovirax®)
- Valacyclovir (Valtrex®; L-valyl ester of acyclovir)
- Famciclovir (Famvir®; diacetyl ester of 6-deoxy penciclovir)

- All suffer from the appearance of resistant HSV mutants

- Fortunately, the mutant strains are less virulent

- The drugs are ineffective against latent virus

Zirgan

Zirgan (0.15% ganciclovir ophthalmic gel)

- FDA approved for herpetic "dendritic ulcers"
- Dosage 1 drop 5x/day until ulcer healed, then t.i.d. x 7 days
- No thimerosal

Another guanosine analog:

- Same mechanism of action as orals

1) competitive inhibition of viral DNA polymerase
2) incorporation and termination of the growing viral DNA chain
3) inactivation of the viral DNA polymerase.

Acyclovir vs. Valacyclovir vs. Famciclovir: What are the Differences?

ZOVIRAX is the brand name for acyclovir, a synthetic nucleoside analogue active against herpesviruses. ZOVIRAX Capsules, Tablets, and Suspension are formulations for oral administration. Each capsule of ZOVIRAX contains 200 mg of acyclovir and the inactive ingredients corn starch, lactose, magnesium stearate, and sodium lauryl sulfate. The capsule shell consists of gelatin, FD&C Blue No. 2, and titanium dioxide. May contain one or more parabens. Printed with edible black ink.

Dosage: 800/400 mg 5x/day AND Lactose

VALTREX (valacyclovir hydrochloride) is the hydrochloride salt of the *L*-valyl ester of the antiviral drug acyclovir.

VALTREX Caplets are for oral administration. Each caplet contains valacyclovir hydrochloride equivalent to 500 mg or 1 gram valacyclovir and the inactive ingredients carnauba wax, colloidal silicon dioxide, crospovidone, FD&C Blue No. 2 Lake, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, povidone, and titanium dioxide. The blue, film-coated caplets are printed with edible white ink.

Dosage: 500 mg tid x 7 day + NO Lactose

FAMVIR tablets contain 125 mg, 250 mg, or 500 mg of famciclovir, together with the following inactive ingredients: hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, polyethylene glycols, sodium starch glycolate and titanium dioxide.

Dosage: 250 mg x7-10 day AND Lactose

Stromal Keratitis Management

2. Stromal Keratitis

a. Without epithelial ulceration

(Therapeutic dose of topical corticosteroid PLUS prophylactic dose of oral antiviral agent)

Prednisolone 1%: 6–8 times daily tapered over greater than 10 weeks **plus**

Acyclovir (Zovirax®): 400 mg twice daily **or**

Valacyclovir (Valtrex®): 500 mg once daily **or**

Famciclovir (Famvir®): 250 mg twice daily

As disease comes under control, prednisolone can be tapered slowly to the lowest possible dose and frequency as determined by the patient's clinical condition. The lower the dose and frequency of topical corticosteroid, the longer the interval between subsequent dose reduction. Oral antiviral agents in **prophylactic** doses (above) should be maintained during corticosteroid treatment.

Stromal Keratitis Management

b. With epithelial ulceration

(Limited dose of topical corticosteroid PLUS therapeutic dose of oral antiviral agent)

Prednisolone 1%: twice daily **plus**

Acyclovir (Zovirax®): 800 mg 3–5 times daily for 7–10 days **or**

Valacyclovir (Valtrex®): 1 g 3 times daily for 7–10 days **or**

Famciclovir (Famvir®): 500 mg twice daily for 7–10 days

The oral antiviral agent is reduced to prophylactic dose and maintained as long as topical corticosteroids are in use. As disease comes under control prednisolone can be tapered slowly. Note: there is no clinical trial data to support a specific recommendation for length of treatment.

Words of Wisdom on HSV

- I **dilate** every patient with suspected ocular herpes regardless of absence or severity of anterior segment findings
- I **warn** patients to come back immediately with any change in vision or increased floaters due to possibility of delayed onset posterior disease
- I **look** for localized and linear KP in all uveitis patients, especially when not in Arlt's Triangle, and subtle corneal edema in known herpes patients, even when they are relatively asymptomatic, as signs of herpes endotheliitis and need for topical steroid in addition to oral antivirals

Blepharitis

Has anyone talked to you in the office about it?

Classification

Anterior

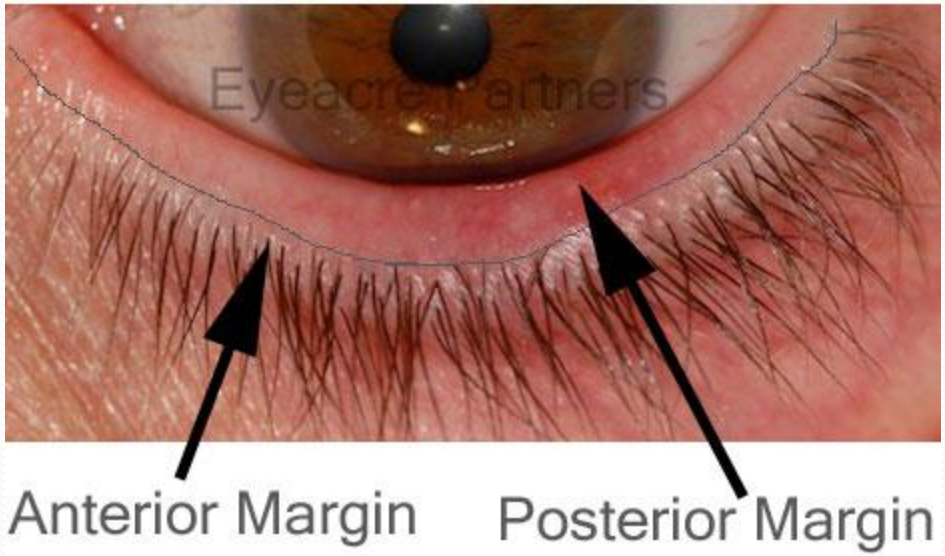
- affects the eyelid epidermis
- base of the eyelashes
- eyelash follicles
  - Staphylococcal
  - Seborrheic blepharitis (scurf)

- **AAO Preferred Practice Guideline: Anterior to Gray Line**

Classification

Posterior

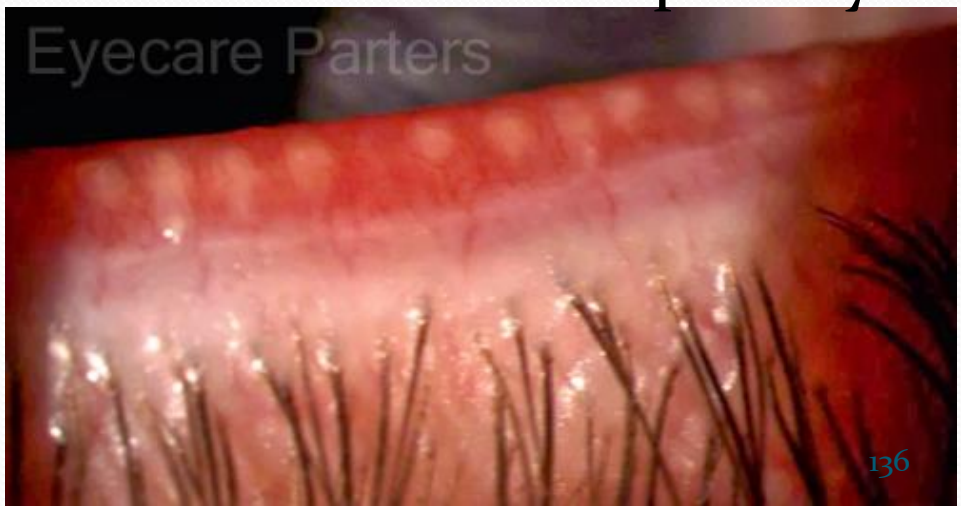
- Inflammation affecting back portion of eyelid margin in relation to the meibomian glands.
- **AAO Preferred Practice Pattern: Posterior to Gray Line**



Classification

Meibomian Gland Dysfunction (MGD)

- Chronic
- Diffuse abnormality of the meibomian gland characterized by terminal duct obstruction and qualitative or quantitative changes in glandular secretion
- Decrease tear film evaporation and deliver an optically stable tear film surface
  - Increased Vulnerability



Hottest Topic Today: Demodex

- Closely associated with Posterior Blepharitis and MGD
- 2 parasitic species
  - Demodex Folliculorum
  - Demodex Brevis
- Beyond 70 years old, 95-100% chance of infestation
- Term used is Cylindrical Dandruff (CD)

95% in 71 to 96 year-old

87% in 51 to 70 year-old

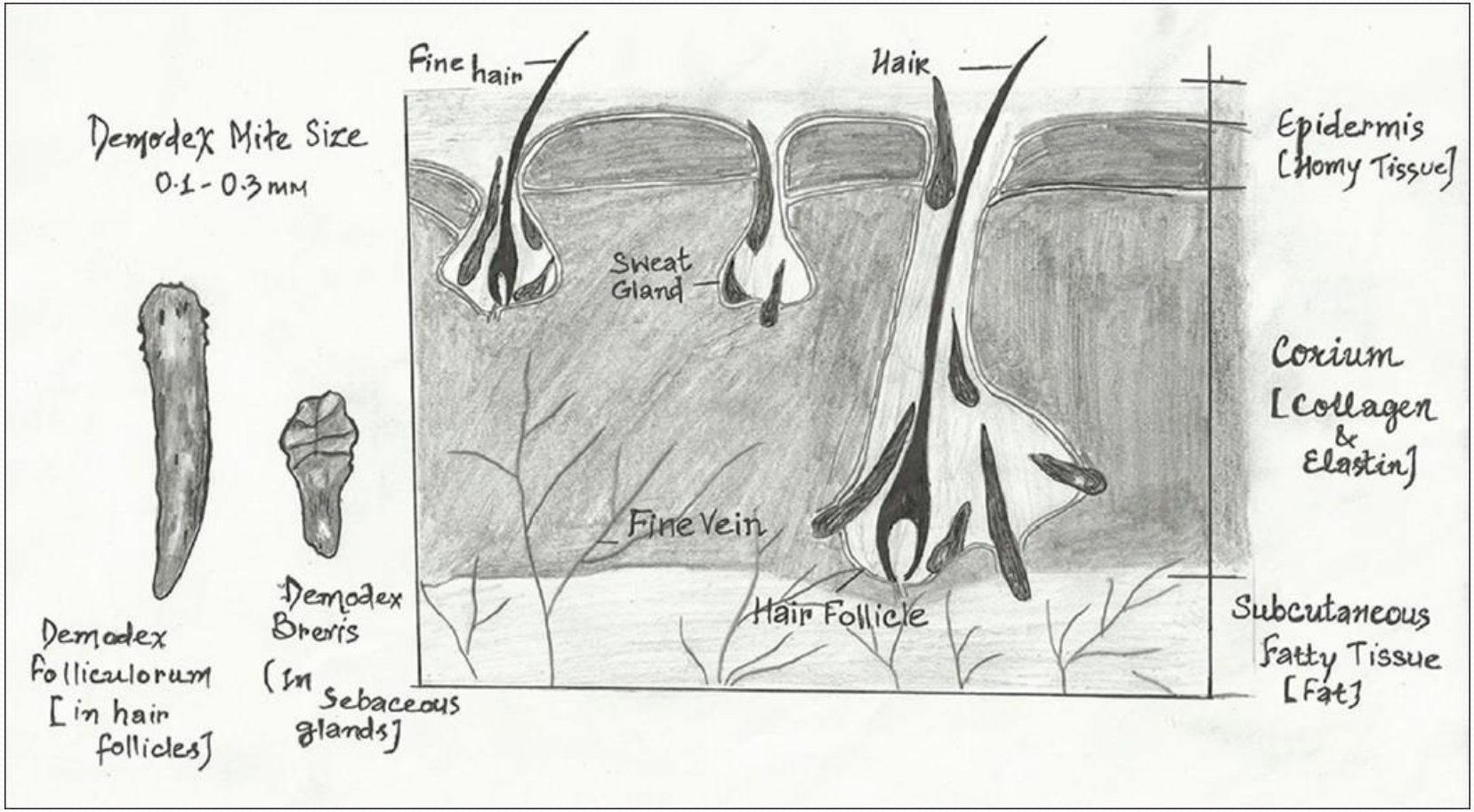
69% in 31 to 50 year-old

34% in 19 to 25 year-old

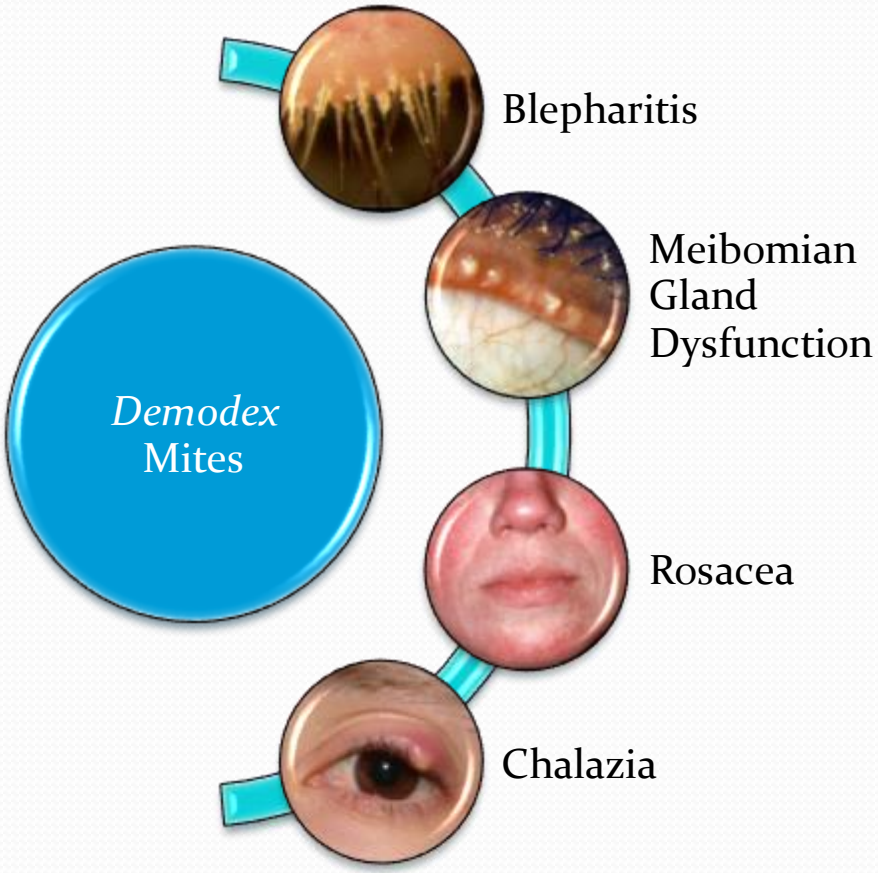
13% in 3 to 15 year-old

The Home of Demodex

- Visualizing the Ectoparasite



Progressive Demodex Events



Fasten Your Seatbelt!

- Explanations for Anterior and Posterior Blepharitis
  - Lumped into 1 group
  - Inefficient oil production and relationship to zits
  - Lifestyle implications with dry eye and “styes”
- Gateway to Makeup discussion
  - Waterproof
  - Placement of mascara line
- Granddaddy is Demodex…

Demodex Patient Conversation

- One of the few times I make a joke to break the ice
  - Start with bacterial portion and then follow that there are some "friends" we all have present in some form or another
  - The next layer of the conversation is why
    - Folliculorum = Lawnmowers for lashes
    - Brevis = Mite Excess Oil Binge Eaters
- Close the loop by sharing the relationship is mostly mutual, but some times we have fights
  - Similar to marriage– we can all get along right?!

Diagnosis and Management Tips

- Established close relationship between Blepharitis and Dry Eye
  - Overlap is 85-86%
  - When Blepharitis progresses, so does Dry Eye signs and symptoms
- Connect the dots for patients.
- Ocular Photography will save time and energy

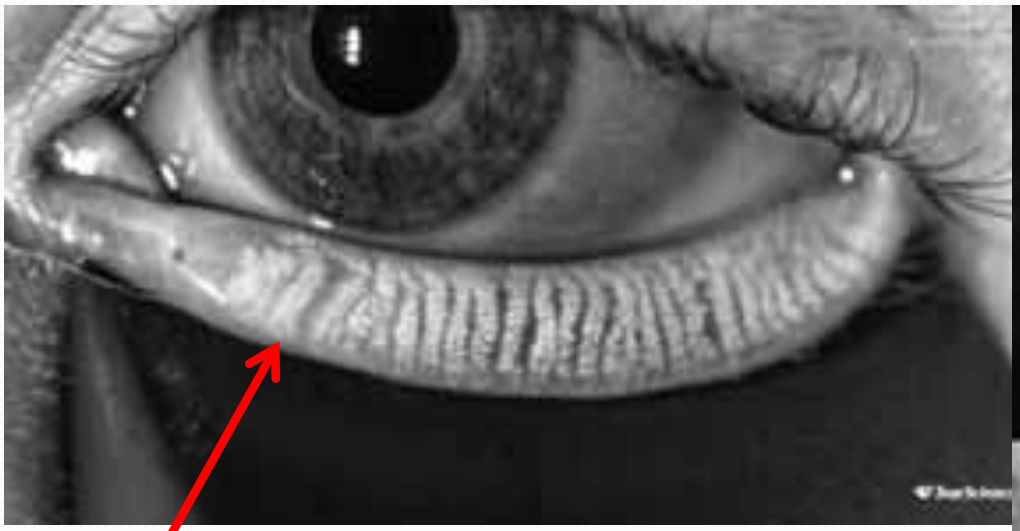
Glaucoma Analogous Testing

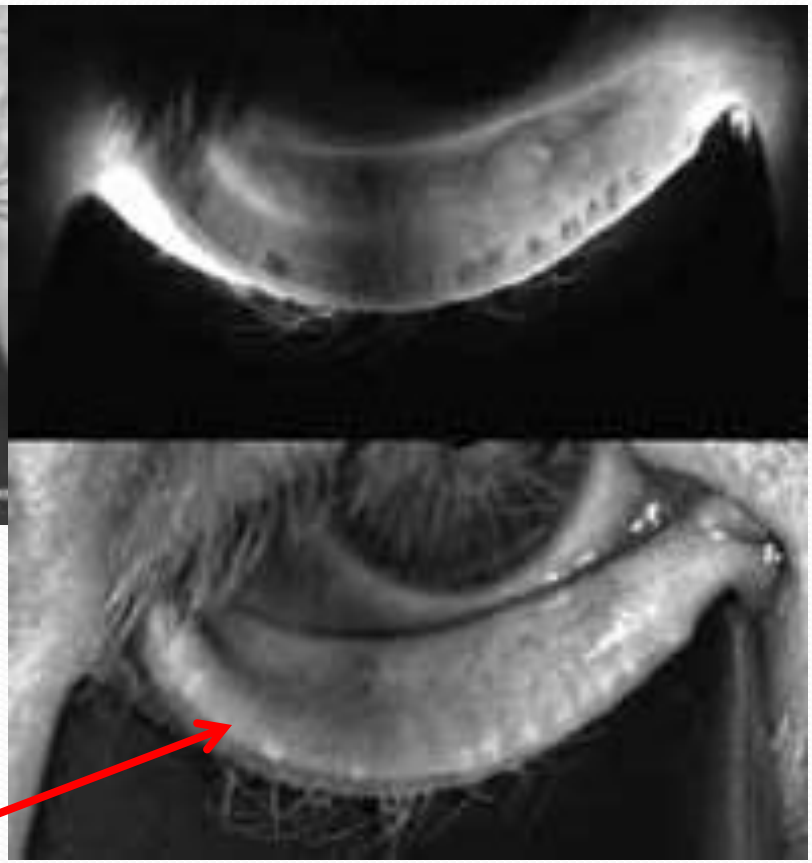
- Structure + Function of the Meibomian Glands and ocular surface

Multiple testing:

- IOP/ORA = Osmolarity
- VF = Corneal staining
- Gonioscopy = TBUT/Tear Meniscus
- OCT = Meibomography/LipiView
- ONH examination = Meibomian Gland expression

LipiView Imagery





Modest Health to Glands

Maximal Dropout of Glands

LipiScan

- Joe Boorady (CEO of TearScience)
  - He is an OD

Device Potential:

- Practice Differentiator
- Unmet need for our peers
- More affordable than purchasing LipiView

Treatment

Mechanical

- Warm Compresses/Lid Massage
- LipiFlow
- MiBo
- IPL
- BlephEx
- Cliradex/Cliradex Light
- Blephadex
- Avenova vs. OCuSOFT HypoChlor
- iLast
- Meibomian Intraductal Probe
- TrueTear?

Medicinal

- Azithromycin (Oral or Drop)
- Doxycycline
- Lipid based artificial tears
- Omega 3's
- Ivermectin/Permethrin
- Tea Tree Oil/Coconut Oil mix
- Restasis (potentially)

The Dental Transformation

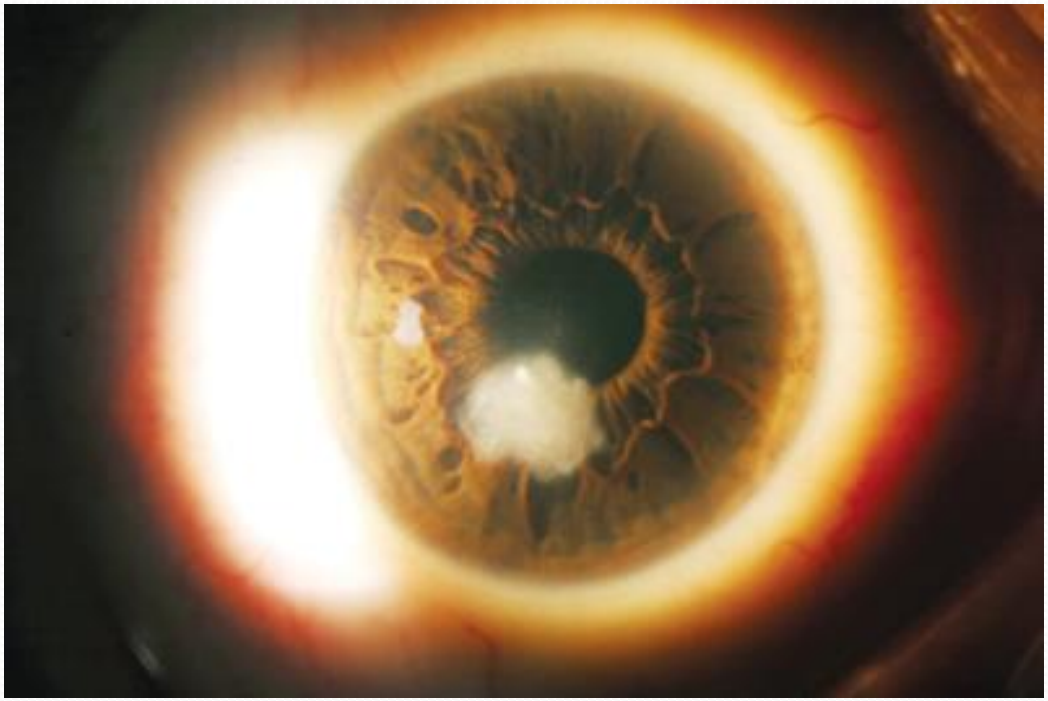
The Dental Model

- It works
- Patients understand it easily

Efficient Analogies:

- Tooth Brush = Warm compress
- Floss = Lid Massage and lid hygiene products
- Scaling = Debridement of keratin with Golf Club Spud
- Dental cleaning = Mechanical pulsation or cleaning
  - LipiFlow, MiBo, BlephEx etc.
- Dental X-rays = Meibography/LipiView

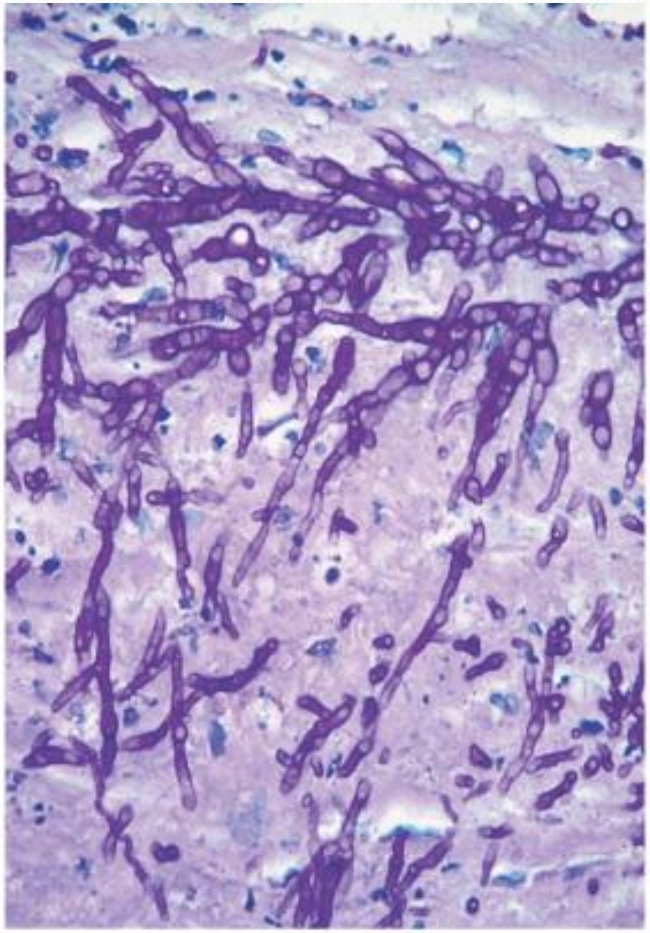
Fungal Keratitis



Remember Fusarium from B+L Renu with MoistureLoc?

Histology

- Eukaryotic
- Fungal hyphae- filamentous
- Branching septate
- Spores
- Penetrate Descemet's without any problem



Risk Factors

- Previous history of ocular trauma (especially if organic matter is involved)
  - 26-100%
- Agricultural occupations
- Age
- Pre-existing ocular disease
- Exposure keratopathy
- Chronic keratitis
- Hydrophilic CL's  Candida
- Chronic use of steroids
- Diabetes
- Systemic immunosuppressive disease
- Humid, Tropical environment

Good News– in most cases…

- Slow movers, more often time than not
- Ill defined lesion compared to sterile infections
  - Dull Gray-white/somewhat fluffy
  - Can have placoid appearance
  - Partial or Total Immune Ring from Fungal Antigen and Host Antibody response
- Typically, even if empirical treatment with antibiotics fails, culturing will reveal entity to initiate the proper therapy
- Know your environment
  - Yeasts = Temperate
  - Filamentous Molds = Tropical, Subtropical

Candida Keratitis

- Yellow-white infiltrate associated with dense suppuration
- Expanding infiltrate in a collar stud configuration
- Endothelial plaque
- Uveitis (maybe)
- Hypopyon (maybe)
- Elevated IOP

Diagnostics

- Blood Tests
  - IgG/IgM/IgA antibodies
  - Real Time PCR
- Plating
  - KOH Stain (Candida albicans)
  - Calcofluor white Stain (Fungi)
  - Gram Stain(Yeast)
  - Chocolate Agar (Bacteria)
  - MacConkey Agar (Oxidase)
  - Trypticase Soy (Bacteria)
  - Giemsa Stain (Filamentous Molds)
  - Sabouraud´s agar culture (Fungi)

Cultures/Systemic Work-Up

- Bacterial
- Viral
- Fungal
- Acanthamoeba
- Chlamydia

- CBC w/ Differential
- ESR/ CRP
- Urinalysis
- Chest X-Ray
- Renal Function tests
- Syphilis
- Hep C
- RF
- ANA
- C-ANCA / P-ANCA
- Tissue Biopsy (Lung / Kidney)

Plating Pearls

- Scrape multiple sites in the ulcer crater,
  - particularly at the margins, to enhance recovery of the organisms
- Use a surgical blade or sterile spatula.
- May need to go rather deep
- When in doubt, collaborate with your local Corneal specialist!

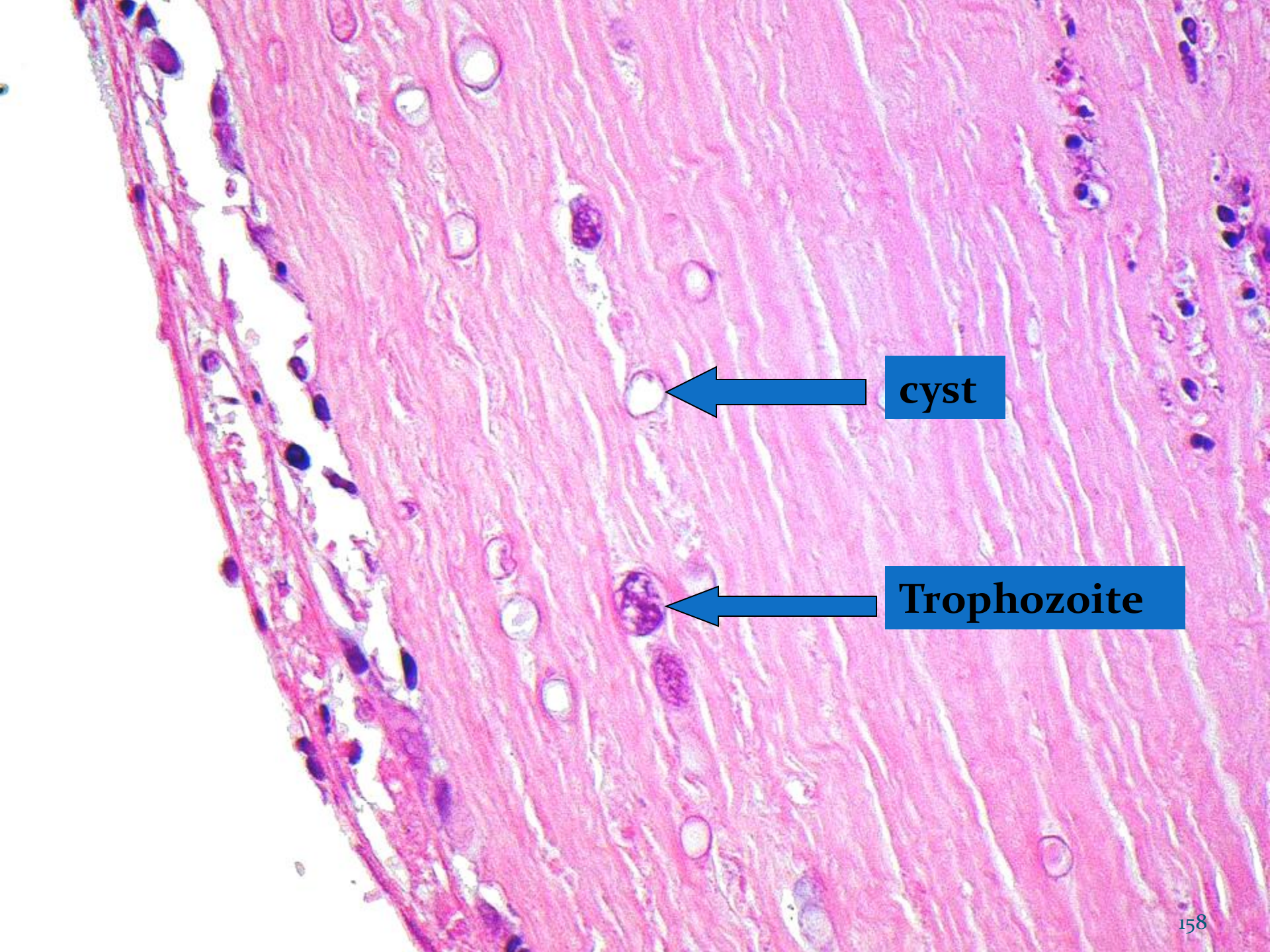
Treatment

- Natacyn (Alcon, Natamycin 5% oph suspension)
  - Commercially available
  - Can be used for Yeast or Filamentous Mold
    - Mycotic Ulcer Treatment Trial (MUTT) did not show superiority with topical Voriconazole 1%
  - Every hour to 2 hours for 3-4 days, then taper dosage depending on presentation14-21 days

Alternatives:

- Compounded Topical amphotericin 0.15% or Topical capsofungin 0.5%
- Therapeutic Graft

Amoebic Keratitis

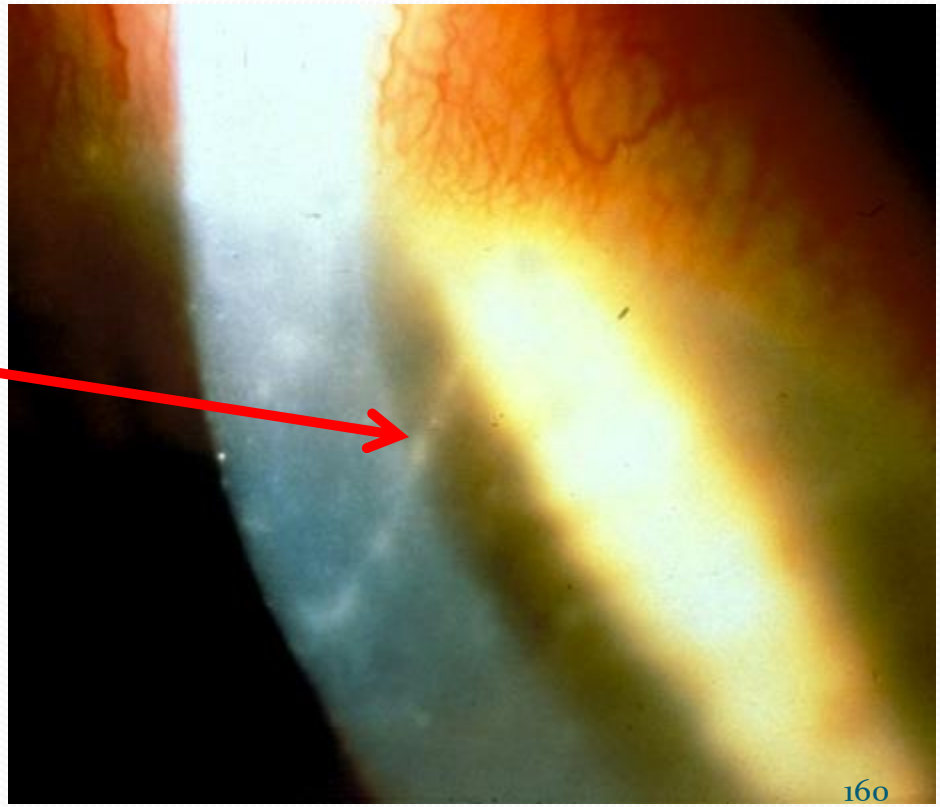

cyst
Trophozoite

Amoeba Characteristics

- 10-50 microns
- Replicate by binary fission
- Exist as trophozoites and cysts
- Trophozoites are active, infectious and feed by phagocytosing.
- Cysts from under hostile conditions and have a double layer.

Clinical Features

- Corneal epithelial trauma predisposes to infection
- Trophizoites attach to damaged epithelium, multiply and cause cytolysis.
- Migrate to stroma-elicit inflammation.
- Trigger keratoneuritis (inflammation follows corneal nerves).



Acanthamoeba Keratitis

- Ubiquitous, warm water
- Homemade contact lens solutions and hot tubs
- Chronic pain and ulcer

- Medications (all off label use): Brolene (0.1% propamidine), PHBG 0.02% , neomycin, miconazole, others.

Notes on Medication Availability

- Brolene not available in US, except from CDC on humanitarian need basis.
- PHBG (polyhexabiguanide) is a swimming pool cleaning chemical, both though an appropriate pool store and filtered/diluted for ophthalmic use.
- Neomycin and miconazole are diluted forms of IV solutions.

None of these medications has a FDA product insert recommendation for use in amoebic keratitis.

This is Us

- We are all human…

  Learning from our mistakes…

  …just like Bruce Wayne.