



DRY EYE SYNDROME

Daryl D. Kaswinkel, MD

March 2022

DRY EYE SYNDROME DEFINED

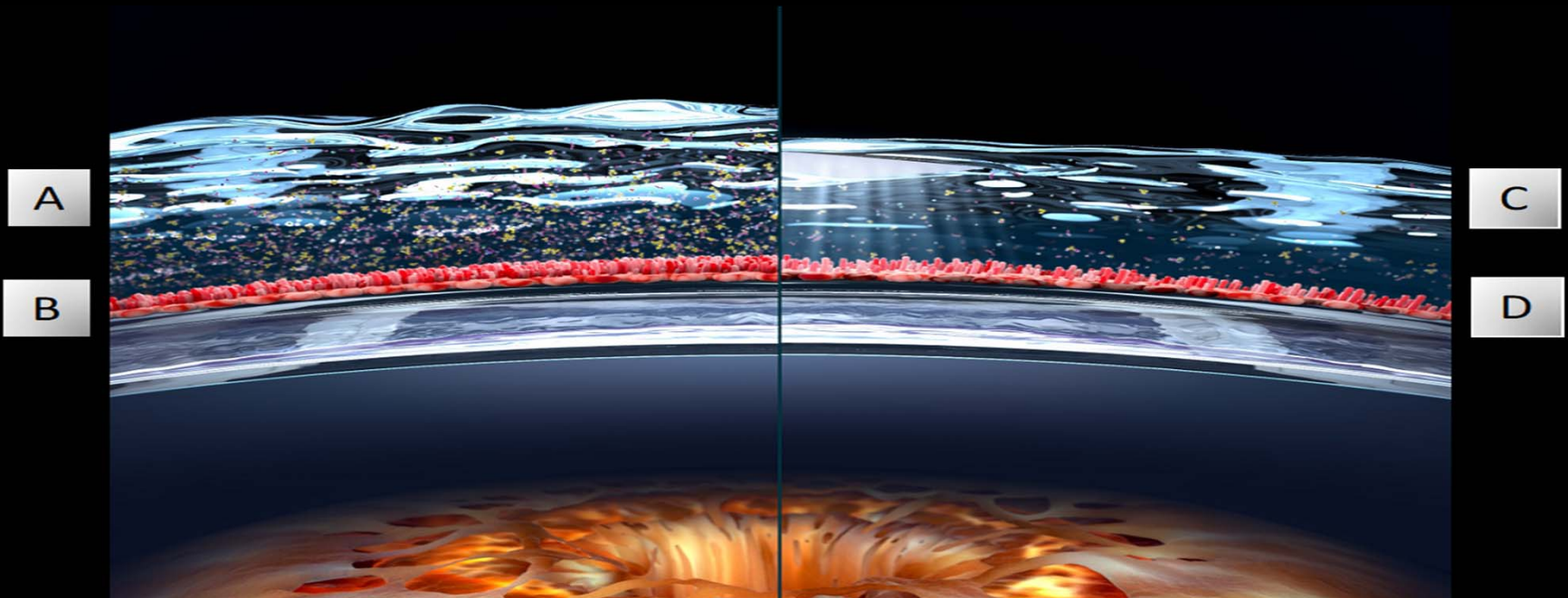
- Clinical Consensus Global Experts (2020)
- Dry Eye Disease (DED) is a *multifactorial* disease
 - Characterized by persistently discomfort and/or visual impairment
 - Accompanied by variable degrees of *ocular surface epitheliopathy, inflammation & neurosensory abnormalities*
- *Tear Film instability* in DED
 - Sensitive measure of tear dysfxn *TBUT, tear break up time*
 - Should be key criterion in clinical definition
- DEWS II (Dry Eye Work-Shop) 2017
- DED is a common, chronic, multifactorial disease of the ocular surface
 - Characterized by a loss of hemostasis of the tear film
 - Accompanied by ocular symptoms, in which tear film instability and , *hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities* play etiological roles.



DRY EYE SYNDROME(DES)

- One of the most common complaints seen by eye professionals
- Nearly 60 million people suffer
- Extremely common in people > 55 yoa
- 2-3 x more common in women than men
- After menopause women who are not on HRT, especially estrogen, more commonly affected

NORMAL & DYSFUNCTIONAL TEAR FILM



A. Solid Lipid Layer, homeostatic distribution of protein, growth factors, electrolytes, and immunoglobulins

B. Abundant Mucins

C. Broken lipid & loss of aqueous volume, fewer proteins, hyperosmolar, more electrolytes

D. Diminished Mucins



PATIENT'S NATURAL TEARS

- Natural tears contain a complex mixture of lipids, proteins, mucins and electrolytes
- Over 1,500 proteins
 - Epidermal Growth Factor (EGF)
 - Transforming Growth Factor(TGF)
 - Nerve growth factors
 - Lysozymes
- 5+ Lipid Classes
- 20+ Mucin Classes
- Electrolytes
- Vitamin A
- Cytokines
- Antibacterial Factors, Immunoglobulins



EPIDEMIOLOGY DES

- Photophobia, sandy or gritty feeling, burning & stinging, itching, dryness, eye fatigue and pain
- Blurry vision, CTL intolerance, mucous discharge, ropy mucous, *Mucous Fishing Syndrome*
- Paradoxical reflex tearing
- Worse later in the day
- Severe cases affecting ADL

PATHOPHYSIOLOGY DES

- Result of many factors contributing to poor tear function
- Often tears hyperosmolar
 - Low aqueous flow
 - excessive tear evaporation
- Hyperosmolarity leads to inflammatory condition
 - Inflammation key consideration in DES
- *T cell infiltration* of lacrimal gland and production of inflammatory cytokines main contributors to inflammatory cascade
- Loss of *parasympathetic stimuli* results in chronic reduction of tear secretion and morphologic destruction of the lacrimal gland



PATHOPHYSIOLOGY DES

- Lacrimal Functional Unit
 - Lacrimal gland, meibomian glands, goblet cells
 - All innervated Parasympathetic via Trigeminal CN
- Tear Film
 - Lipid layer, outer most, prevents evaporation
 - Meibomian glands & minor accessory glands
 - Aqueous layer, middle layer
 - Lacrimal glands and accessory
 - Mucin layer- inner most, stability and even distribution of tear film across surfaces.
 - Goblet cells

DES ETIOLOGY

- Aqueous Deficient
 - Sjögren related
 - Rheumatoid Arthritis(RA)
 - Systemic Lupus Erythematosus(SLE)
 - Non- Sjögren Related
 - Age related
 - 2nd to lacrimal gland infiltration
 - AIDs, Sarcoidosis, lymphoma

DES ETIOLOGY- CONTINUED

- Aqueous Deficient
 - Non-Sjögren related
 - Sensory Block
 - Refractive surgery including *Corneal Crosslinking(CXL)*, *Corneal Transplantation(DALK/PKP especially CXLed or limbal stem deficiency related to contact lens*, Contact Lens, & HSK
 - Damage to cranial nerve V (trigeminal)
 - Motor Block
 - Anti-cholinergic medications
 - Damage to cranial nerve VII (facial)



DES ETIOLOGY- CONTINUED

- Evaporative Causes
 - Meibomian gland dysfxn, ocular rosacea, isotretinoin (Accutane)
 - Eyelid disorders: thyrotoxicosis, poor eyelid apposition esp elderly, *Floppy Eyelid Syndrome*
 - Blink Disorders: Parkinson's Disease & Stroke
 - Ocular Surface disease: allergic conjunctivitis



DIAGNOSIS DES

- Criteria for Diagnosis vary.
- Patient have different tolerability to ocular discomfort
- Some significant clinical DES & few complaints
- Others minor physiological changes & more symptoms

DES TESTING

- *Fluorescein staining* (100%)
- *TBUT* , Tear Break-Up Time(94%)
- Schirmer's(71%)
- Lissamine green & Rose Bengal (65%)
- Corneal Topography (41%)
- Impression cytology- goblet cells(24%)
- Tear Fluorescein Clearance(24%)
- Questionnaire(<10%)
- Tear Osmolarity(<10%)
- Conjunctival Biopsy(<10%)



TREATMENT GUIDELINES

- Grading Severity
 - based on Signs and Symptoms
 - Recommend treatment protocols

Non Pharmacological

- Environmental Changes
- Hypoallergenic products
- Water intake
- Pharmacological



TREATMENT GUIDELINES

- Pharmacological
- Primary Treatment: Artificial Tears
 - Provide palliative treatment without addressing underlying pathophysiology of DES
 - Long list of available agents
- Discontinuing OTC medications, esp. allergy medications

TREATMENT GUIDELINES

- Eyelid Hygiene – MGDysfxn
 - Warm Compresses, Non-irritating Soaps (*Cetaphil*)
- Nutritional Supplements: Omega 3, Lovaza
- Corticosteroids ≤ 4 weeks
 - *Eysuvis 0.25 %* & compounded Methylprednisolone
 - Decrease corneal staining and inc. goblet cells
- Punctal Plugs – provide pooling of tears
 - After anti-inflammatory controlled
- Therapeutic CTL – Bandage Contact Lens with/without AMT(amniotic), Boston Scleral Lens

TREATMENT GUIDELINES

- Cyclosporine –Restasis (0.05%) & Cequa (0.09%)
 - Increase in Schirmer's
 - May lessen progression of DES
 - Helps control inflammatory cascade via T-Cell therefore hyperosmolarity in DES
- Xiidra-Lifitegrast
 - Helps control inflammatory cascade via T-Cell
- Oral Tetracycline and Topically Azasite –
 - promote proper lid fxn, anti –inflammatory inhibition of matrix (metallo)proteinase or inflammatory cytokines, inflammatory cascade
 - Oracea (sustain released), avoid Minocycline (Lupus Syndrome)
- NSAIDs – decrease in filaments, risk corneal sensitivity



TREATMENT GUIDELINES

- Tarsorrhaphy
- Acetylcysteine (Mucomyst compounded)
 - Dec. filaments
- Seretagogues
 - Cholinergic: Oral pilocarpine, side effects
- Investigational
 - Topical androgens



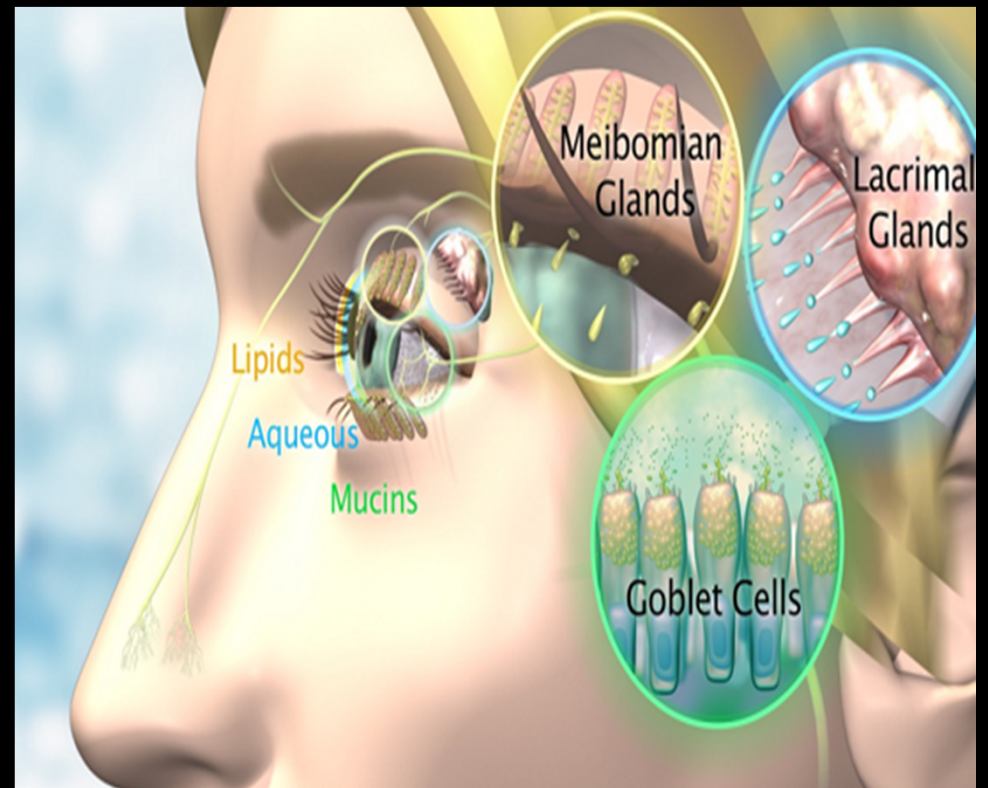
TYRVAYA (VARENICLINE)

- Approved October 15, 2021
- Cholinergic agonist indicated for the treatment of DED
- Preservative-free delivered as a 0.05 ml spray of 0.03mg solution
- One spray, each nostril twice a day (~12 hours apart)
- Onset of action and sustained outcomes after 5 minutes
- Most common adverse reaction was sneezing, other adverse reactions >5% cough, throat irritation, and instillation-site (nasal) irritation

PARASYMPATHETIC NERVOUS SYSTEM (PNS) CONTROLS OF TEAR FILM HOMEOSTASIS

The trigeminal nerve is accessible w/in the nasal cavity and is activated by Tyrvaya nasal spray by activation of cholinergic receptors

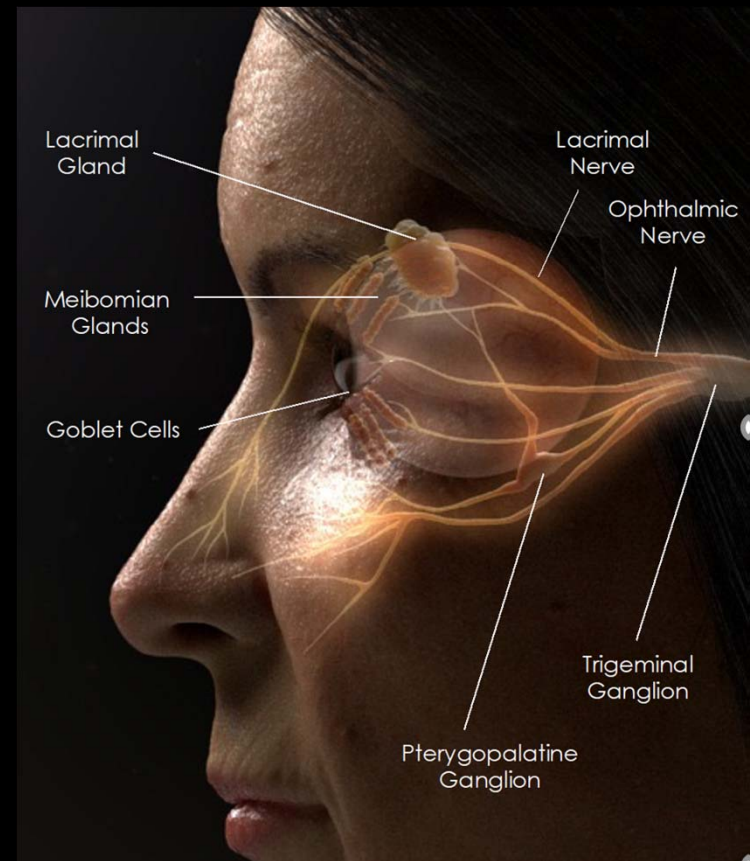
PNS stimulation of LFU activates basal tear film.
34% of basal tears by nasally inhaling air



LACRIMAL FUNCTIONAL UNIT

The LFU is innervated by the trigeminal nerve

Chronic reduction of tear secretion and morphologic destruction of the lacrimal gland with loss of parasympathetic stimuli





AUTOLOGOUS *SERUM (BLOOD) TEARS*

Compounded Medications

March 2022

AUTOLOGOUS SERUM (BLOOD)TEARS

- Looking at the complexity of tear film, simple substitution of an artificial tear product will not provide the same relief as natural components of the patient's own tear film.

- **Autologous Serum (Blood) Tears**



AUTOLOGOUS SERUM (BLOOD)TEARS

- Serum = fluid component of whole blood which remains after clotting
- 1980's Fibronectin in serum as wound healing agent, 1984 Fox Study Benefits in DES
- All components of tears that are thought to be beneficial are also present in serum
- Unpreserved and non-antigenic



TEAR FILM

- Provides critical lubrication, optical qualities, nutrients, foreign body and microbe removal and anti-bacterial and wound healing substances to the avascular cornea.
- Ideal Tear Substitute = provide epitheliotrophic support in addition to lubrication



ARTIFICIAL TEARS

- Pharmaceutical tear replacements - Artificial Tears
 - Optical
 - Mechanical
- What about?
 - Anti-microbial
 - Nourishing

Autologous Serum (Blood) Tears

	Unstimulated Tears	Serum
pH	7.4	7.4
Osmolality	298	296
EGF(ng/ml)	0.2-3.0	0.5
TFG(ng/ml)	2-10	6-33
Vitamin A (mg/ml)	0.02	46
Lysozyme(mg/ml)	1.4	6
IgA	1190	2

SERUM: FIBRONECTIN, HEPATOCYTE GF, NGF, GF-1, SUBSTANCE P, COMPLEMENT, FIBROBLAST GF, IGS

AUTOLOGOUS SERUM (BLOOD)TEARS

- Revival after report of successful treatment of persistent epithelial defects, Tsubota, 1999
- Studies: persistent epithelial defects, Recurrent Erosion Syndrome, SLK, adjunctive treatment ocular surface reconstruction (Large Diameter Deep Anterior Lamellar Keratoplasty, DALK)

Slide 28

DK1

Daryl Kaswinkel, 3/19/2022

AUTOLOGOUS SERUM (BLOOD)TEARS

- Kojima, Am J Ophthalmology 2005; 139:242-6
 - Prospective randomized case-control trial
 - severe dry eye patients
 - 2 weeks wash out, randomly assigned 2 groups
 - Only preservative free artificial tears
 - autologous 20%-50% serum tears 6x/day
 - Improvement mean TBUT, F/RB staining scores, and subjective symptom scores in Autologous Serum Tears group

AUTOLOGOUS SERUM (BLOOD) TEARS

- Future:
 - Umbilical Cord Serum Eye Drops
 - Yoon AAO September 2007, Vol 114, Number 9, pp 1637-1942
 - Even more promise than Serum(Whole Blood)Tears

AUTOLOGOUS SERUM (BLOOD)TEARS

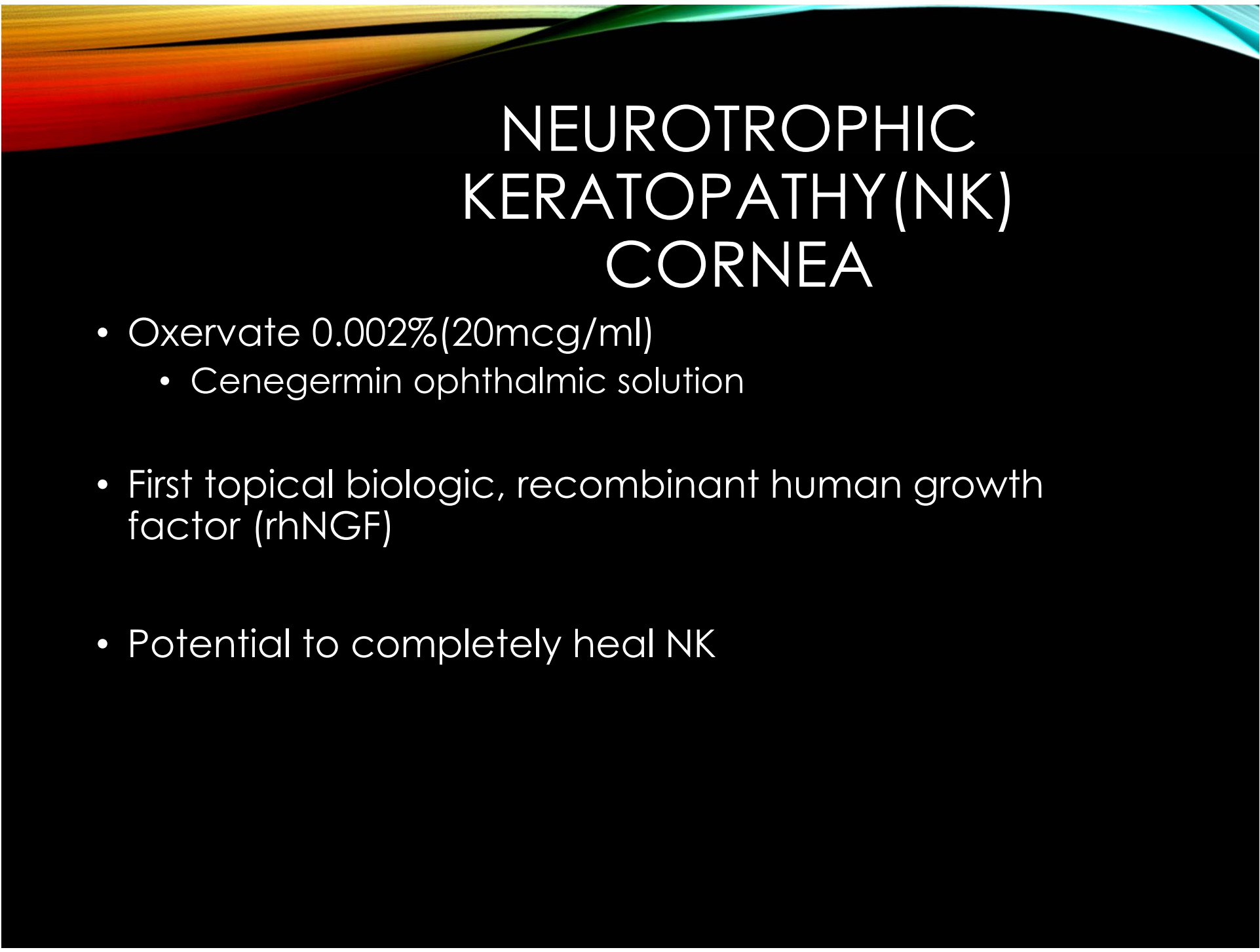
- Conclusion(s):
- Ideal for patients and viable alternative
 - Severe Symptoms and/or Signs of DES
 - Also mild and moderate cases unresponsive to other intervention
 - Complicated DES esp. complicated by
 - Persistent Epithelial Defects, Recurrent Erosion Syndrome, SLK, Adjunctive in Ocular Surface Reconstruction (Limbal Stem cell transplants, Amniotic Membrane grafts, PKPs, LVC (LASIK)



CORNEA BIOLOGIC - *OXERVATE*

Dompé US/Italy Inc.

March 2022



NEUROTROPHIC KERATOPATHY(NK) CORNEA

- Oxervate 0.002%(20mcg/ml)
 - Cenergermin ophthalmic solution
- First topical biologic, recombinant human growth factor (rhNGF)
- Potential to completely heal NK



BIOLOGIC THERAPIES

- Use of living organisms, substances from living organisms or laboratory produced versions of such substances to treat diseases
- Biologics therapies stimulate or suppress immune system in fight cancer, infection, and other diseases
 - Retina: Avastin (bevacizumab) targets vascular endothelial growth factor (VEGF)
 - Diabetic Retinopathy/Macular Degeneration

NK

- NK rare and progressive eye disease lead to scarring and vision loss
 - ~65,000 patients in USA affected
- Conditions leading to NK:
 - Herpetic infections
 - Dry Eye Disease
 - Ocular or Neurosurgical Procedure: *Corneal Transplantation(DALK/PKP especially CXLed or limbal stem deficiency related to contact lens*
 - Systemic Conditions impairing corneal Sensation (CVD – Primary or Secondary Sjögren's Syndrome)



OXERVATE – HOW IT WORKS

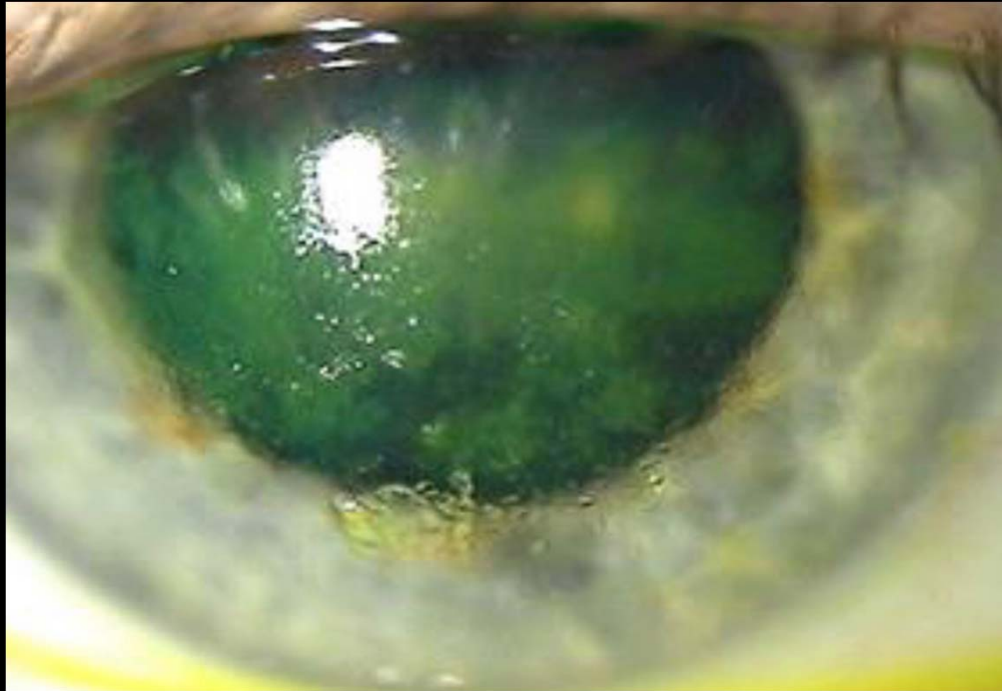
- Cornea ~7,000 nerve endings/mm²
- Nerves mediate blinking/tearing reflexes vital in maintaining corneal health
- Nerves also produce nerve growth factor (NGF), supporting nerve themselves and corneal epithelium
- NGF stimulates proliferation and differentiation of cornea epithelial cells and promotes tear production to lubricate and protect the eye



OXERVATE – HOW IT WORKS

- NGF promotes corneal nerve growth lost in NK
- Oxervate's active ingredient is recombinant form of human nerve growth factor (rhNGF), protein with identical structure to naturally occurring NGF

STAGES OF NK- MILD



- Stage 1: Ocular Surface Irregularity and reduced vision

STAGES OF NK - MODERATE



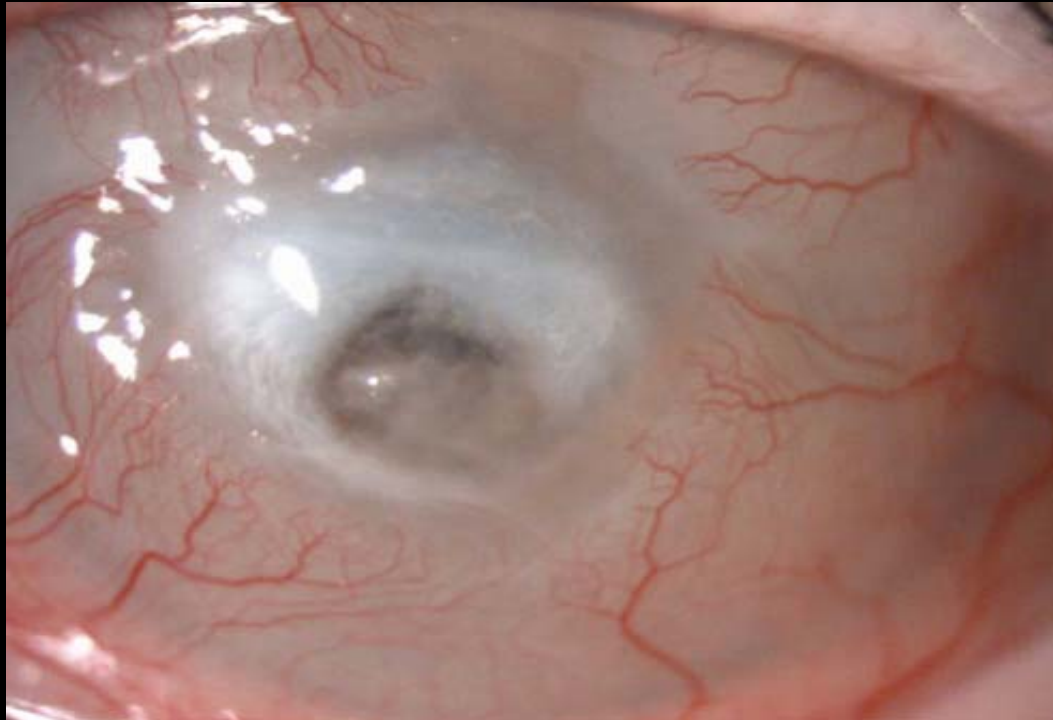
- Stage 2: non-healing persistent epithelial defect (PED)

STAGES OF NK - SEVERE



- Stage 3: Corneal ulceration involving the sub-epithelial (stromal) tissue

STAGES OF NK



- Ultimately Corneal melting/perforation
 - Descemetocoele

KEY FINDINGS

- Majority of patients in clinical studies with topical Oxervate well tolerated and more effective in promoting complete corneal healing of moderate or severe NK
- 2+6=8
 - Every 2 hours w/a at least 6 times a day for 8 weeks
 - 65 to 72 % completely healed
 - 80% remained healed for one year



ACTHAR SYSTEMIC BIOLOGIC

Mallinckrodt Pharmaceuticals

March 2022

ACTHAR

- Corticotrophin injection for severe allergic and inflammatory eye conditions.


MENU

Ophthalmology CENTER
FOR HEALTHCARE PROFESSIONALS

H.P. **Acthar**[®] GEL
(repository corticotropin injection) 80 U/mL

**Acthar: FDA-approved
for a range of severe
acute and chronic
allergic and
inflammatory
ophthalmic conditions**



ACTHAR

- ACTHar – repository corticotropin injection 80U/ml
- Medicine for severe acute and chronic allergic and inflammatory conditions affecting the eye, from cornea, iris, retina and optic nerve.
 - Especially **Dry Eye Disease** and uveitis whether idiopathic or autoimmune/inflammatory related to underlying systemic process.
 - *Corneal Transplantation(DALK/PKP especially CXLed or limbal stem deficiency related to contact lens) and Cornea Transplant Rejection (< w/ DALK over PKP)*
 - Cornea rejection or related systemic disease

ACTHAR

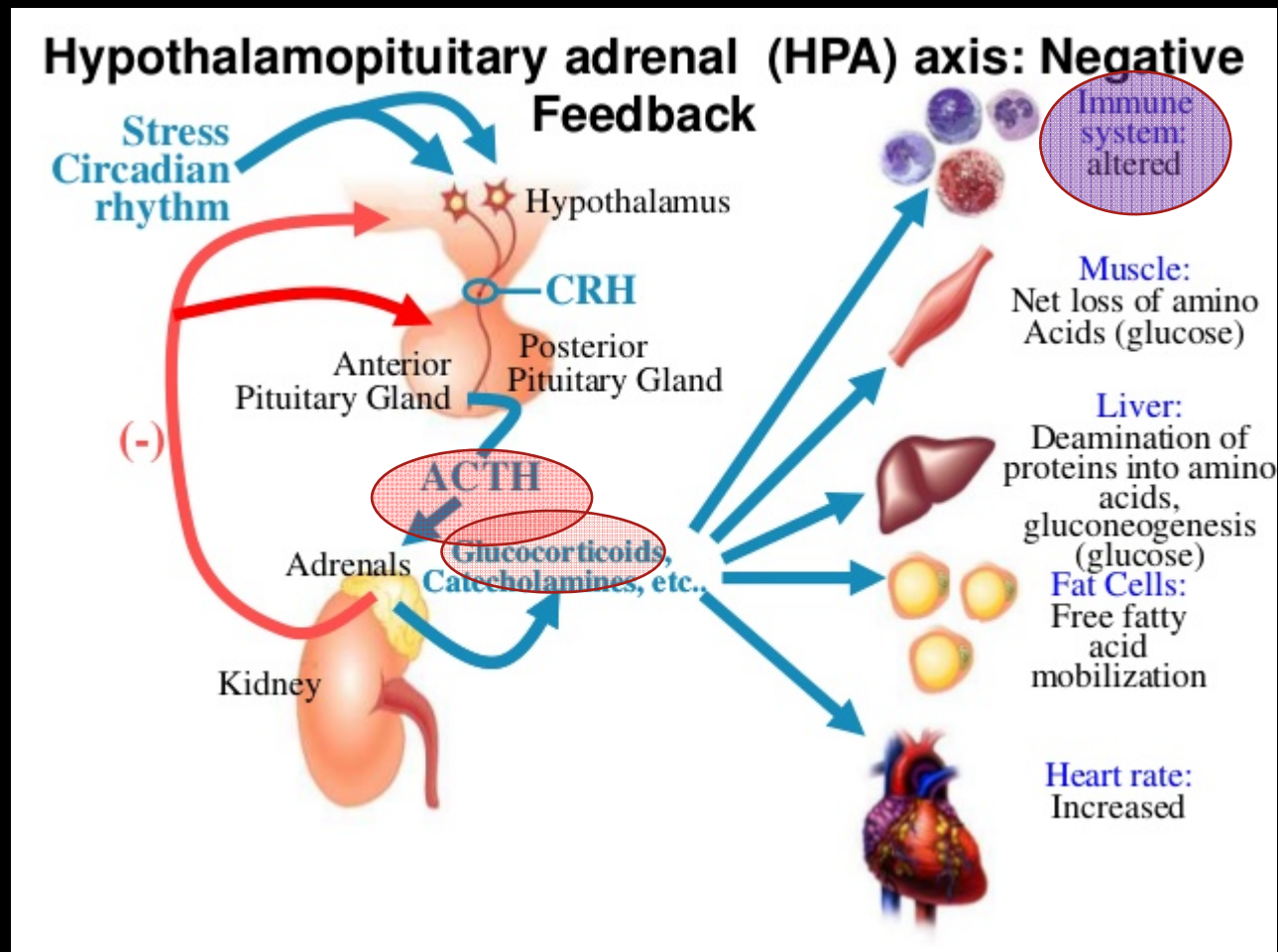
- ACTHAR – injection is given subcutaneously or intramuscularly so as to provide prolonged release
- Dosing – individualized according to severity of disease process
- Usual dose 40 to 80 units every 2 to 3 days
- Key Benefit: ACTHAR reduces the unwanted systemic side effects of oral corticosteroids with the same if not better immunosuppression.



HOW ACTHAR BELIEVED TO WORK

- Biologic Agent contains hormone ACTH, adrenocorticotrophic hormone
- Directly modulates immune system to control inflammatory and immune processes
- Not a steroid however monitor for side effects as corticosteroids.
 - Cushing's syndrome, adrenal insufficiency, intestinal bleeding, hypertension, diabetes, osteoporosis

HOW ACTHAR BELIEVE TO WORK





THANK YOU

