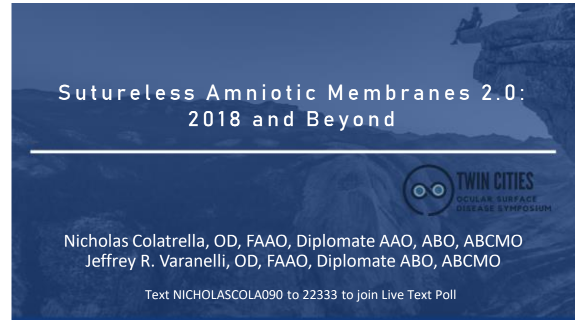
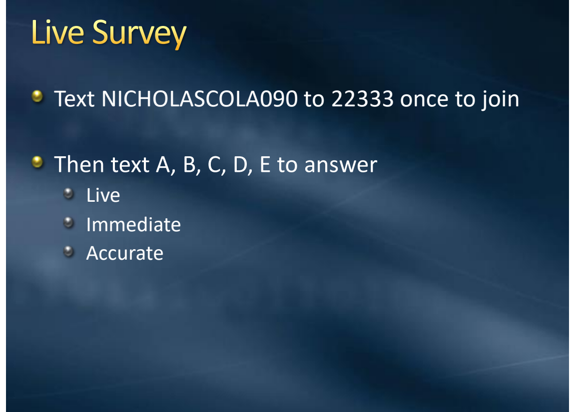
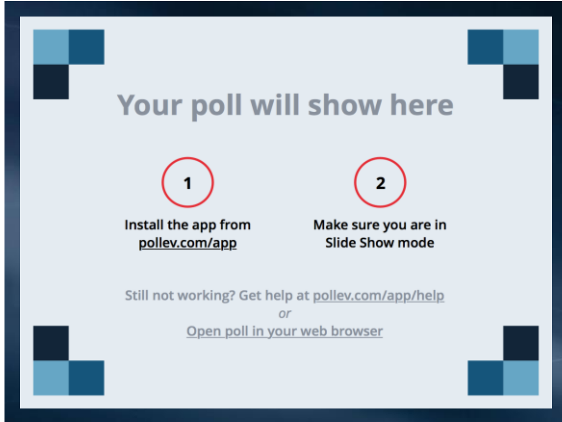

Sutureless Amniotic Membranes 2.0: 2018 and Beyond
TWIN CITIES
OCULAR SURFACE DISEASE SYMPOSIUM
Nicholas Colatrella, OD, FAAO, Diplomate AAO, ABO, ABCMO
Jeffrey R. Varanelli, OD, FAAO, Diplomate ABO, ABCMO
Text NICHOLASCOLA090 to 22333 to join Live Text Poll

TWIN CITIES
OCULAR SURFACE DISEASE SYMPOSIUM
Disclosures
• Allergan Pharmaceuticals Speaker's Bureau
• Shire Pharmaceuticals
• Bio-Tissue
• BioDLogics, LLC
• Katena/IOP
• Seed Biotech
• Johnson and Johnson Vision Care, Inc.


Live Survey
Text NICHOLASCOLA090 to 22333 once to join
Then text A, B, C, D, E to answer
Live
Immediate
Accurate

Nicholas Colatrella, OD, FAAO, Dipl AAO, ABO, ABCMO
Jeffrey Varanelli, OD, FAAO, Dipl ABO, ABCMO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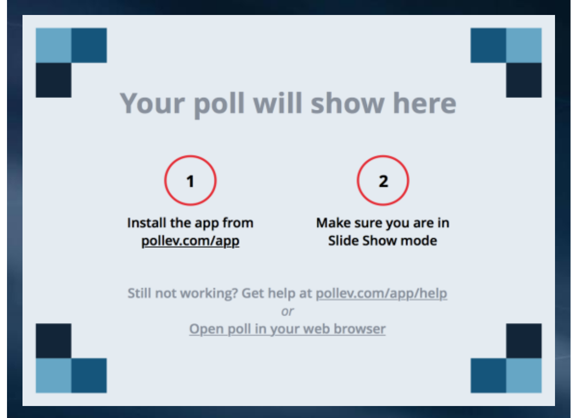
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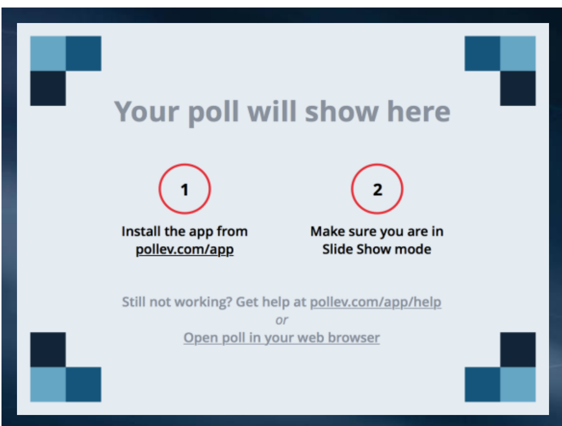
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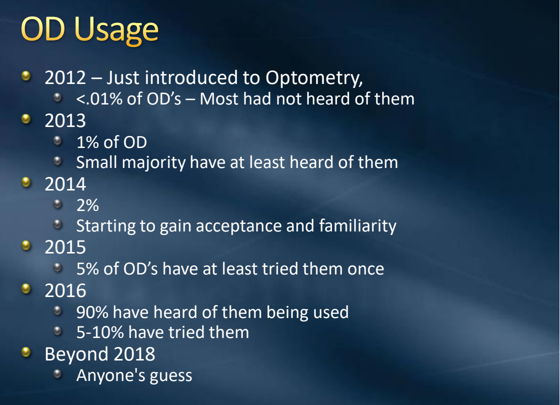
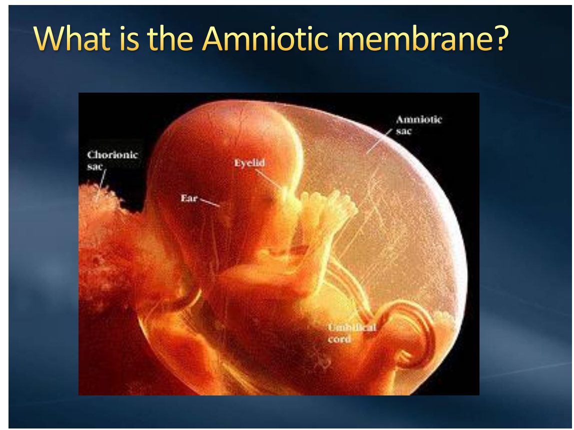

OD Usage
2012 – Just introduced to Optometry,
<.01% of OD's – Most had not heard of them
2013
1% of OD
Small majority have at least heard of them
2014
2%
Starting to gain acceptance and familiarity
2015
5% of OD's have at least tried them once
2016
90% have heard of them being used
5-10% have tried them
Beyond 2018
Anyone's guess

2.0 Lecture was based on your previous comments
Please add more detailed information on the course of how and when to follow up with these patients
Please explain what we will see clinically during the process of treatment/follow up.
Please speak of details of treating bilateral conditions, max length of wearing time?
Evidence of how beneficial this is

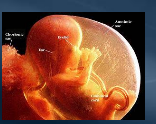
2.0 Lecture was based on your previous comments
Please give more information regarding complete treatment plan.
Please spend more time on how to insert and remove the lenses and follow up protocols while in place etc….
Please give some information regarding scope of practice for different states regarding using amniotic membranes.

Biologic Therapies
Any therapy that uses living organisms to treat and fight disease
monoclonal antibodies
vaccines, including therapeutic vaccines
blood and blood products for transfusion and/or manufacturing into other products
gene therapies
cell therapies
Cancer Treatments
Insulin
Hormone replacement therapy
Premarin
Rheumatoid Arthritis
Enbrel
Remicade
Humira
Macular Degeneration
Macugen
Avastin
Lucentis
Eylea


What is the Amniotic membrane?
Amniotic sac
Chorionic sac
Eyelid
Ear
Umbilical cord

What is the Amniotic membrane

- Thin but tough transparent pair of membranes, which hold a developing embryo (and later fetus) until shortly before birth.
- The primary function of the amniotic membrane is to protect the fetus from injury.
  - 1. Anti-inflammatory
  - 2. Anti-scarring
  - 3. Anti-angiogenic



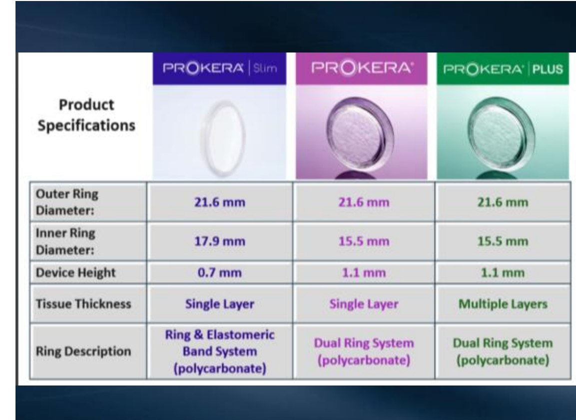
Amniotic membrane

- Amnion is avascular and a translucent membrane composed of an inner layer of epithelial cells which are planted on a basement membrane
- Amnion is made of Collagen I, III, IV, V and VII, laminin and fibronectin of which IV, VII, laminin and fibronectin are also found in conjunctiva and cornea

Mechanisms of Action

- Promotes Epithelialization
- Suppresses Inflammation
- Inhibits Scarring
- Inhibits Angiogenesis
- Neurotrophic Factors
- Anti-Microbial Agent

All without the harmful side effects found in topical and oral medications



Product Specifications	PROKERA Slim	PROKERA	PROKERA PLUS
Outer Ring Diameter:	21.6 mm	21.6 mm	21.6 mm
Inner Ring Diameter:	17.9 mm	15.5 mm	15.5 mm
Device Height	0.7 mm	1.1 mm	1.1 mm
Tissue Thickness	Single Layer	Single Layer	Multiple Layers
Ring Description	Ring & Elastomeric Band System (polycarbonate)	Dual Ring System (polycarbonate)	Dual Ring System (polycarbonate)

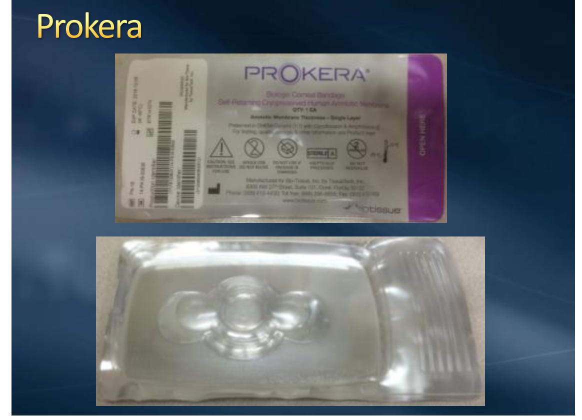
Prokera

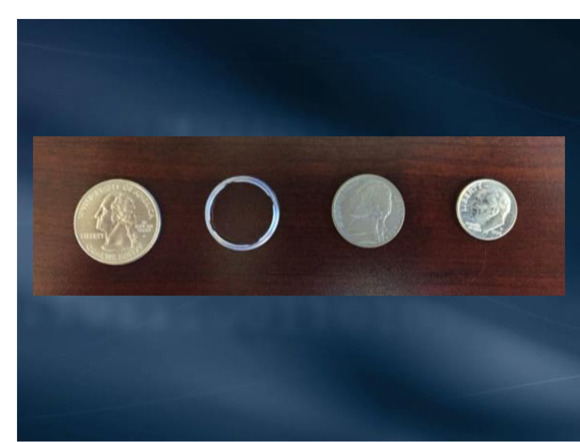
- Approved by FDA Dec 2003 as a Class II medical device comprised of cryopreserved amniotic membrane graft fastened to thermoplastic ring-set
  - Launched in April 2005
  - 17,000 milestone in September 2014
- Dual action promotes healing of ocular surface and controls inflammation

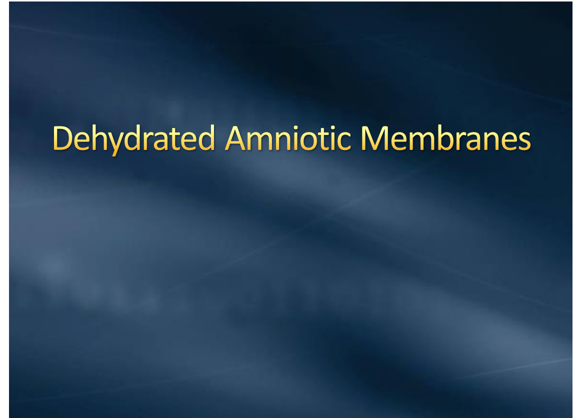
- Stored in medium made of Dulbecco's Modified Eagle Medium / Glycerol containing Ciprofloxacin and Amphotericin B
  - Do not use on patients with a history of drug Rxn to Cipro or amphotericin B

Prokera

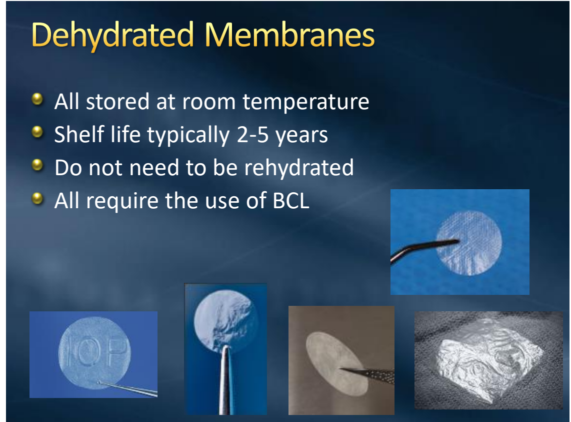
- Cryopreserved
- Store in refrigerator x 3 months 1° C to 10° C (33.8° F to 50°F)
- Store in freezer
  - 1 year between -49° C to 0° C (-56.2° F to 32° F)
  - 2 years between -85° C to -50° C (-121° F to -58° F)
- Shelf life is 2 years from date of manufacturer
- Allow to thaw to room temperature unopened for 5-10 min
- Open inner pouch and keep in tray to irrigate
- Rinse with BSS / saline to reduce stinging sensation
- Do not leave in eye longer than 30 days

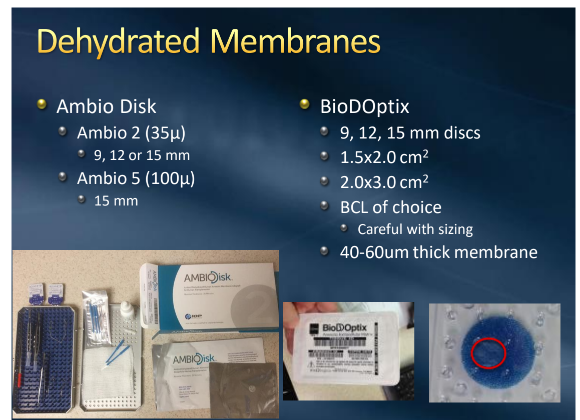


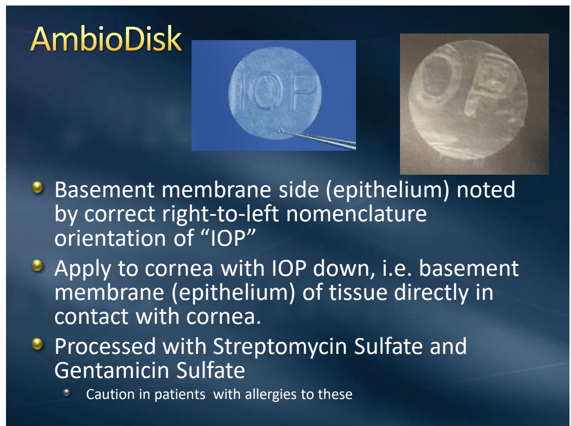


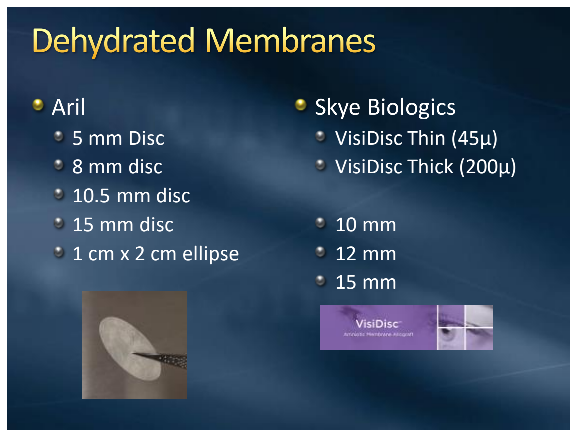


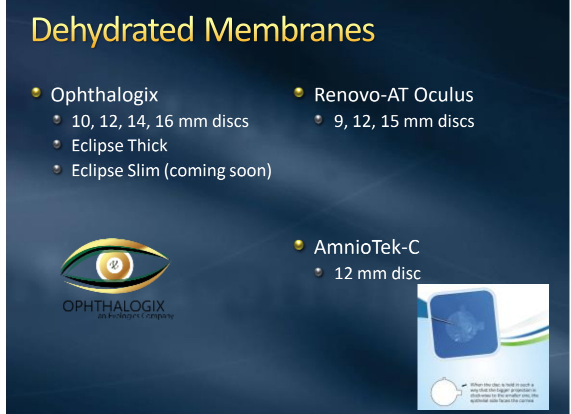
AmbioDisk (IOP Inc. / Katena)
BioDOptix (BioDLogics)
Aril (Seed Biotech)
VisiDisc (Skye Biologics)
ReNovaAT (RegenMed)
AmnioTek-C (ISP Surgical LLC)
Ophthalogix (EvoLogics)

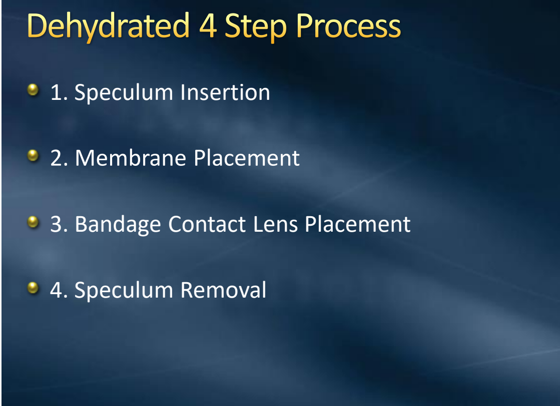


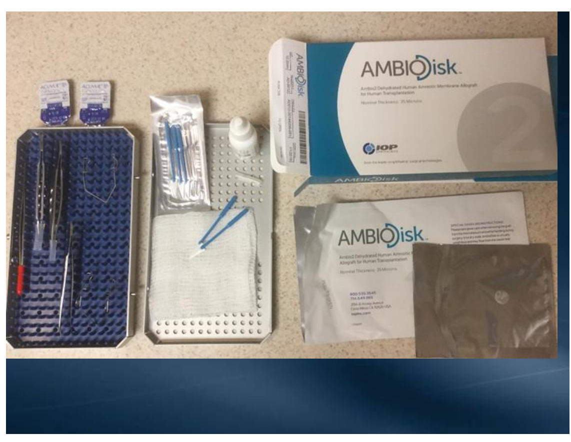


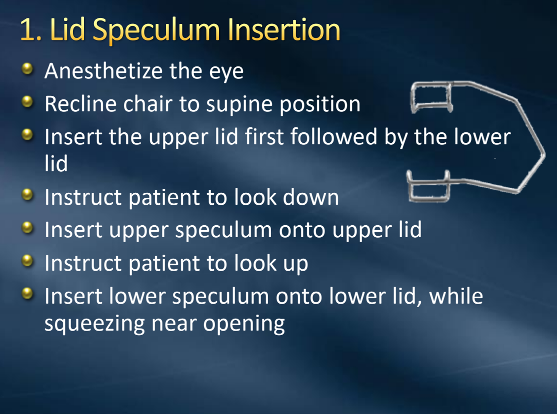

AmbioDisk
IOP
Basement membrane side (epithelium) noted by correct right-to-left nomenclature orientation of “IOP”
Apply to cornea with IOP down, i.e. basement membrane (epithelium) of tissue directly in contact with cornea.
Processed with Streptomycin Sulfate and Gentamicin Sulfate
Caution in patients with allergies to these

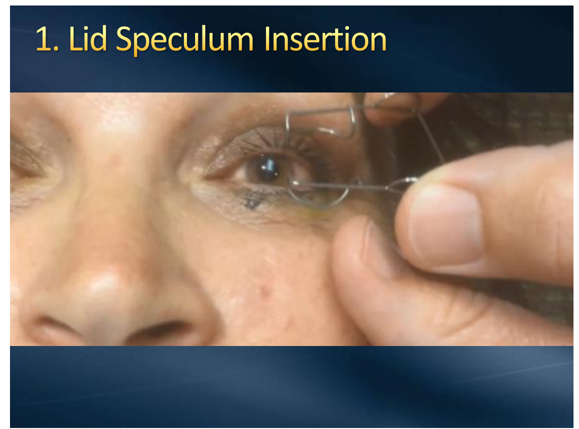

Dehydrated Membranes
Aril
5 mm Disc
8 mm disc
10.5 mm disc
15 mm disc
1 cm x 2 cm ellipse
Skye Biologics
VisiDisc Thin (45µ)
VisiDisc Thick (200µ)
10 mm
12 mm
15 mm
VisiDisc

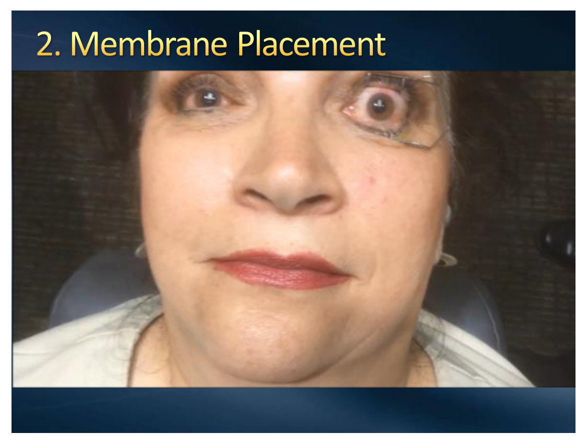

Dehydrated Membranes
Ophthalogix
10, 12, 14, 16 mm discs
Eclipse Thick
Eclipse Slim (coming soon)
Renovo-AT Oculus
9, 12, 15 mm discs
AmnioTek-C
12 mm disc
OPHTHALOGIX


Dehydrated 4 Step Process
1. Speculum Insertion
2. Membrane Placement
3. Bandage Contact Lens Placement
4. Speculum Removal

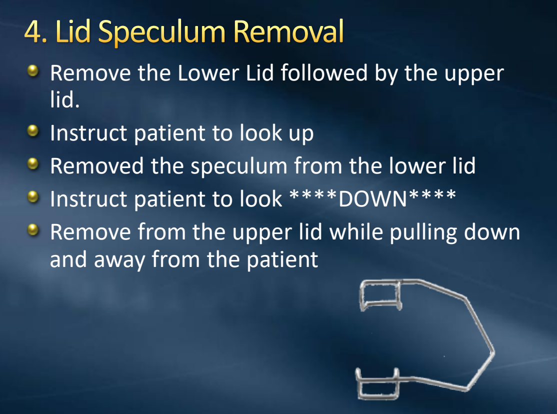

AMBIODisk
IOP
AMBIODisk


1. Lid Speculum Insertion
Anesthetize the eye
Recline chair to supine position
Insert the upper lid first followed by the lower lid
Instruct patient to look down
Insert upper speculum onto upper lid
Instruct patient to look up
Insert lower speculum onto lower lid, while squeezing near opening

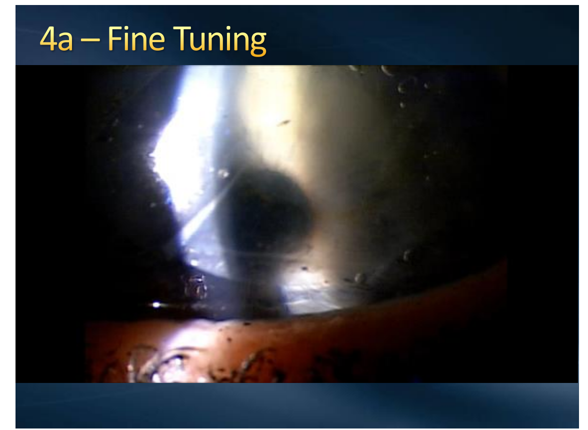

1. Lid Speculum Insertion


2. Membrane Placement

3. Bandage Contact Lens Placement


4. Lid Speculum Removal
Remove the Lower Lid followed by the upper lid.
Instruct patient to look up
Removed the speculum from the lower lid
Instruct patient to look ****DOWN****
Remove from the upper lid while pulling down and away from the patient

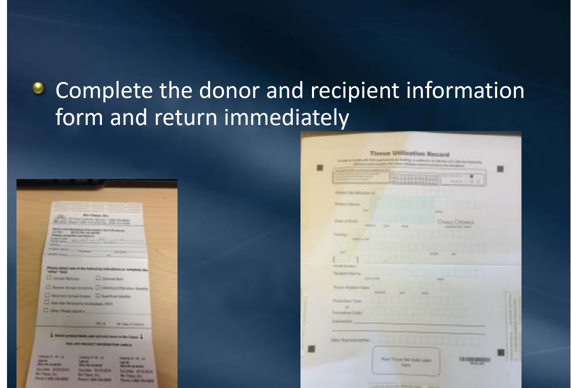
4. Lid Speculum Removal


4a – Fine Tuning

Suggestions

- Create a routine for using these
- Consent Form
- Home going instructions help
  - Antibiotic
  - Corticosteroid
  - Cycloplegic
  - Oral narcotic
- Debridement prior
- Follow up call
- Dropbox link to consent form, etc
  - https://www.dropbox.com/sh/5sb1pyaxl734vtq/AAAyNeW2ujTtvcSZL7CGSubKa?dl=0

- Complete the donor and recipient information form and return immediately



Indications

- Acute Chemical Burns
- Recurrent Corneal Erosions
- Neurotrophic Defects / Persistent Corneal Epithelial Defects
- Filamentary Keratitis
- Vernal Keratoconjunctivitis
- Recalcitrant Dry Eye
- Microbial Keratitis
- Nodular Degeneration
- PRK Haze
- Corneal Neovascularization
- Thermal Corneal Burns

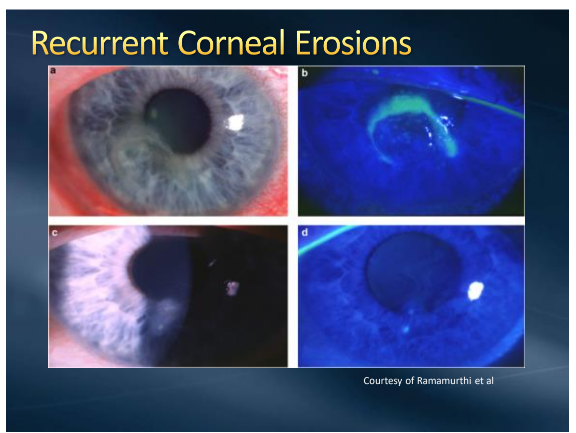
Indications

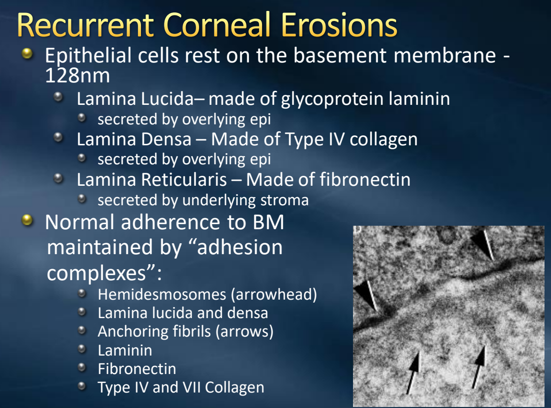
- Acute Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis
- Post-infectious Recalcitrant Corneal Inflammation (e.g. herpetic, vernal, and bacterial)
- In conjunction with:
  - Superficial Keratectomy
  - High-Risk Corneal Transplantation
  - Corneal ulcers, descemetocele or perforations
  - Scleral melts
  - Limbal graft for partial or total limbal stem cell deficiency
  - Oculoplastic procedures including lid, fornix, and socket reconstruction
  - Glaucoma Surgery
  - Conjunctivochalasis and conjunctival reconstruction
  - Pterygium surgery
  - Bullous keratopathy
  - Band keratopathy

Side Effects

- Do not achieve desired result
- Contact lens slippage or displacement of Prokera Ring
- Blurry Vision
- Burn and sting upon instillation
- Too uncomfortable for patient to tolerate
- Membrane dissolves too quickly
  - Need thicker membrane
- Membrane doesn't dissolve
  - Typically due to CL being too tight
    - Recommend checking K values prior to insertion and find appropriate BSCL
- Created irritation to cornea (almost micro burns)
  - Sensitivities to chemical make up of cryo / dehydration process

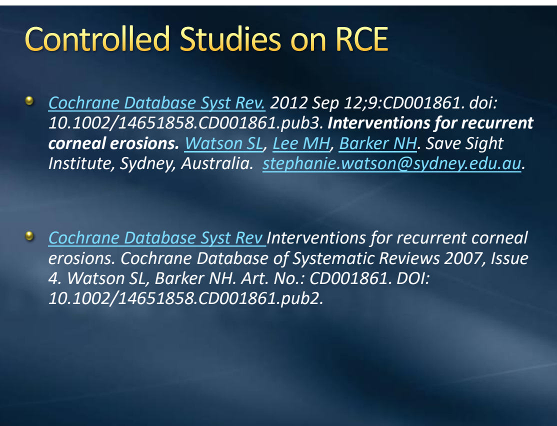
Recurrent Corneal Erosion H18.839

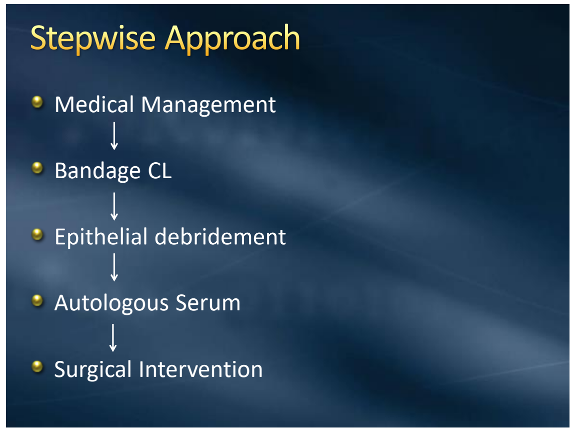


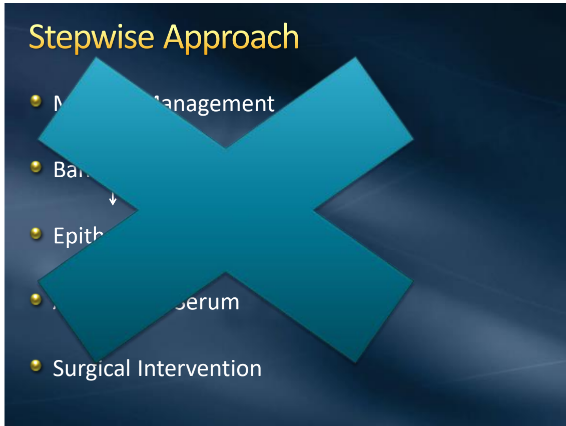


Recurrent Corneal Erosions

- Matrix metalloproteinase (MMP)
  - Name for group of enzymes that break down the structure of the extracellular matrix (collagenase)
  - Gelatinase
    - Composed of MMP-9 and MMP-2
    - Degrades collagen type IV and VII and Laminin
      - all major components of BM
- Elevated levels of MMP-9 and MMP-2 have been observed in tears of patients with RCE
- Increased MMP-9 and MMP-2 expression have been implicated in the pathogenesis of RCE's
  - upregulation may lead to BM degradation and poor epithelial basement membrane adhesion.
- Higher than required levels of MMP may dissolve old and newly forming BM



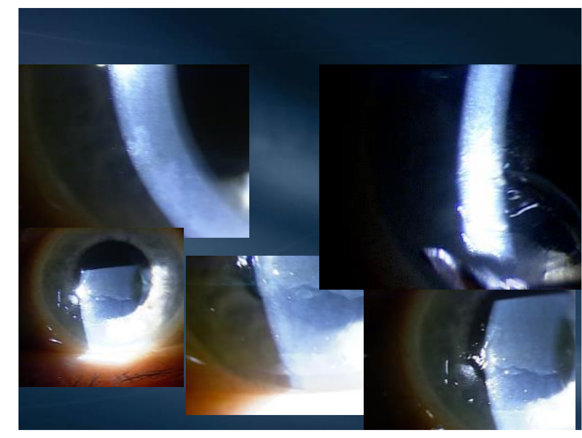


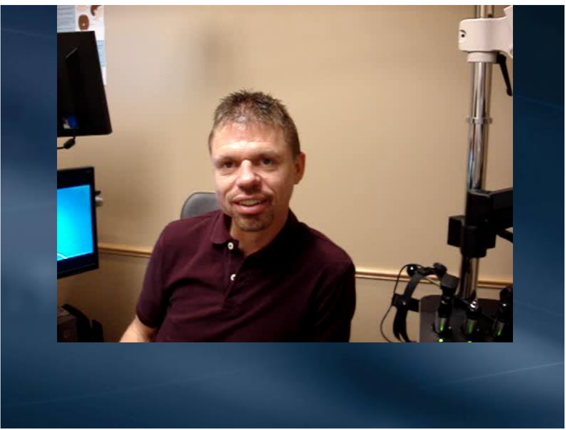


Combination Approach

- Best option is a combination Tx with a minimum of 4 individual tx options
- Trial and error to find the best combo for each patient
  - Epi debridement >>> Amniotic Membrane >>> >>> Autologous Serum >>>DCN
  - Epi Debridement >>> EW BSCL 12 weeks >>> DCN >>> Lotemax
  - ASP >>> BSCL 12 weeks >>> DCN >>> Lotemax

- 45 year old white male– Marathon runner
- October 2012: First visit seen on emergent basis
  - Scratched OD by his Dog
  - 2 linear abrasions detected
    - Healed as expected, Educated on possibility of RCE
- February 2013: RCE but reports minor events on and off for last couple of months
  - EW BSCL
- April 2013: RCE and on and off for weeks
  - EW BSCL and DCN
- Oct 2013: RCE
  - EW BSCL, DCN, Azasite, Muro

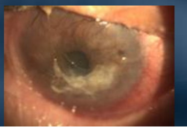




- Day 1 follow up
  - Epithelium healing in
  - Membrane fully intact
  - Continue gatifloxacin QID, Pred Forte QID
- Day 3 follow up
  - Epithelium almost completely healed
  - Membrane dissolving. Open centrally
- Day 7 follow up
  - Removed Prokera ring and placed an EW BSCL
  - Continue Pred Forte QID for 1 week
  - Continue gatifloxacin QD prophylactic

Persistent Corneal Epithelial Defects / Neurotrophic Defects

- An epithelial defect is defined as persistent when it has failed to heal within a 2 week period.
- (PED) occur when there is a failure of the mechanisms promoting corneal epithelialization.
  - results in disassembly of hemidesmosomes accompanied by degradation of Bowman's layer and stroma



Persistent Corneal Epithelial Defects / Neurotrophic Defects

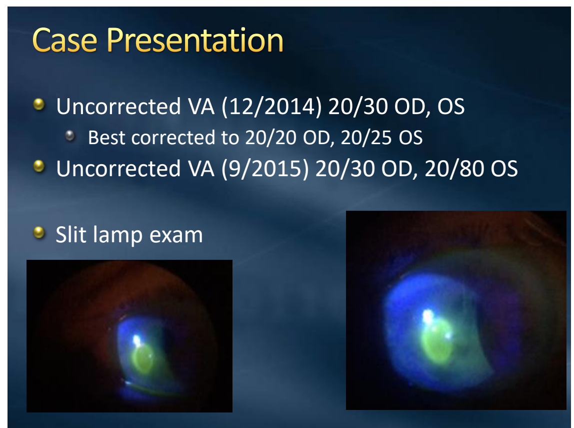
- PED commonly occur in patients with:
  - Neurotrophic corneas
  - LSCD such as chemical injury
  - immune-mediated ocular surface disorders including atopic keratoconjunctivitis
  - ocular mucus membrane pemphigoid
  - Stevens–Johnson Syndrome
  - Peripheral ulcerative sclerokeratitis

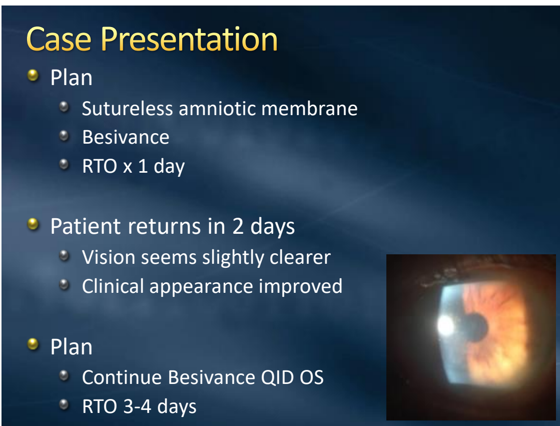
Neurotrophic Keratopathy

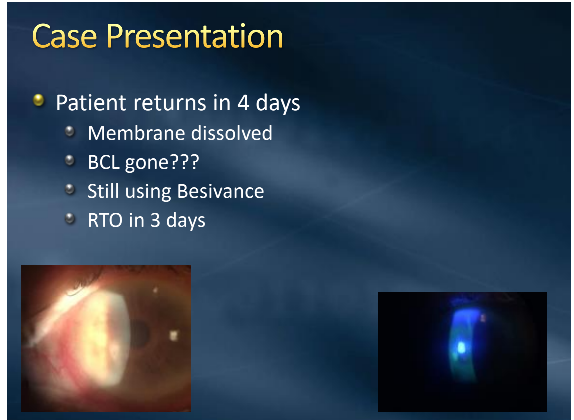
- Results from impaired corneal innervation
- Causes
  - Most common
    - Herpes Simplex or Herpes Zoster
    - Trigeminal Nerve Surgery
    - Acoustic Neuroma
- May be more common in diabetic patients
- Likely will have depletion of Substance P

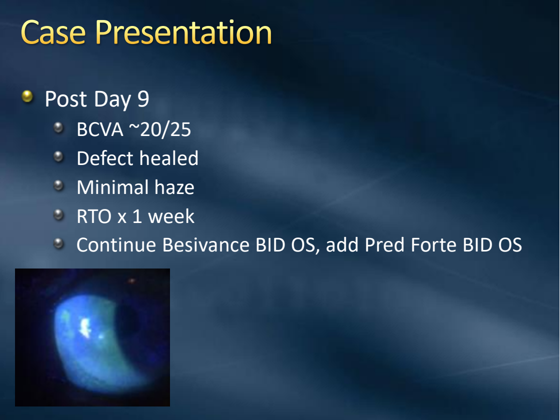
Case Presentation

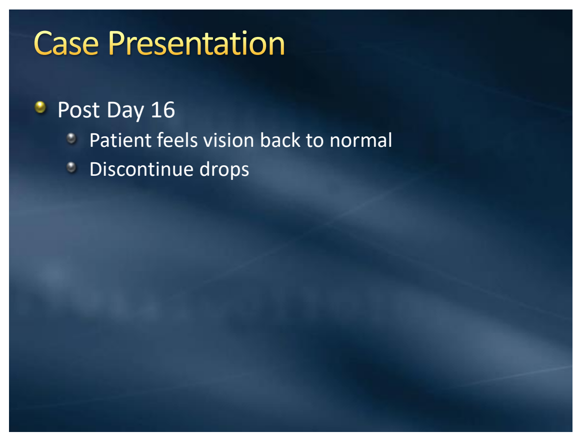
- RM, 81 year old Caucasian male
- Presents with c/o blurred vision OS x 1 month
- Medical History
  - Type II Diabetes
  - Hyperlipidemia, hypertension
  - Chronic kidney failure
- Ocular history
  - Cataract surgery 10+ years ago
- Surgical history
  - Tonsillectomy
  - Trigeminal nerve surgery for cluster headaches

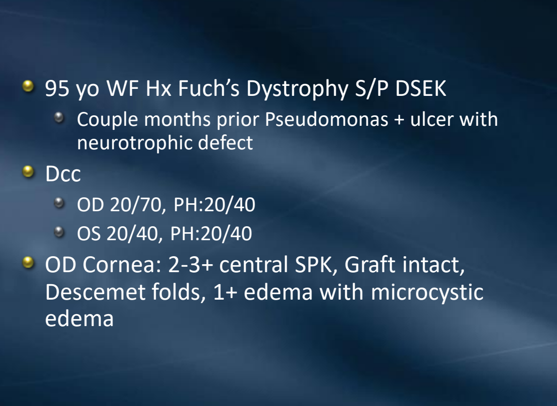

Case Presentation
Uncorrected VA (12/2014) 20/30 OD, OS
Best corrected to 20/20 OD, 20/25 OS
Uncorrected VA (9/2015) 20/30 OD, 20/80 OS
Slit lamp exam

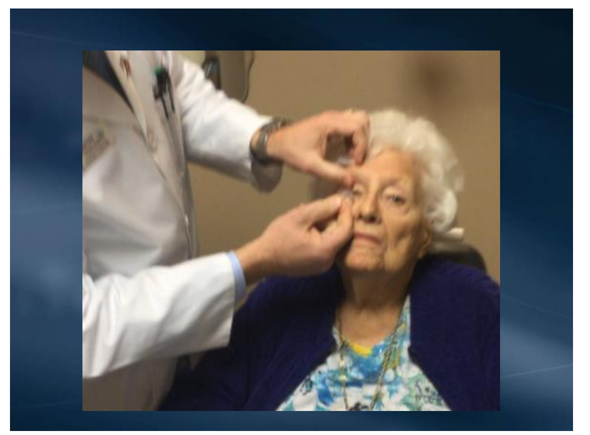

Case Presentation
Plan
Sutureless amniotic membrane
Besivance
RTO x 1 day
Patient returns in 2 days
Vision seems slightly clearer
Clinical appearance improved
Plan
Continue Besivance QID OS
RTO 3-4 days


Case Presentation
Patient returns in 4 days
Membrane dissolved
BCL gone???
Still using Besivance
RTO in 3 days


Case Presentation
Post Day 9
BCVA ~20/25
Defect healed
Minimal haze
RTO x 1 week
Continue Besivance BID OS, add Pred Forte BID OS


Case Presentation
Post Day 16
Patient feels vision back to normal
Discontinue drops


95 yo WF Hx Fuch's Dystrophy S/P DSEK
Couple months prior Pseudomonas + ulcer with neurotrophic defect
Dcc
OD 20/70, PH:20/40
OS 20/40, PH:20/40
OD Cornea: 2-3+ central SPK, Graft intact, Descemet folds, 1+ edema with microcystic edema

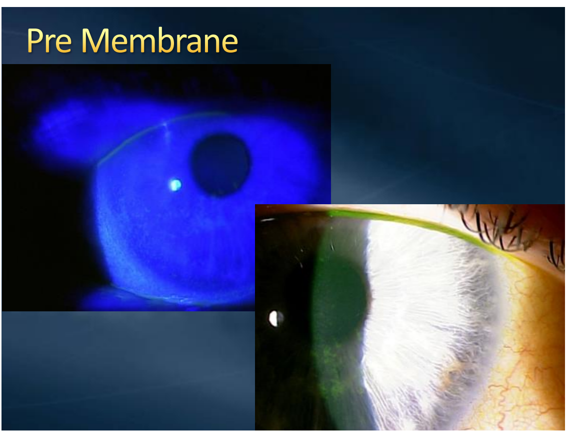


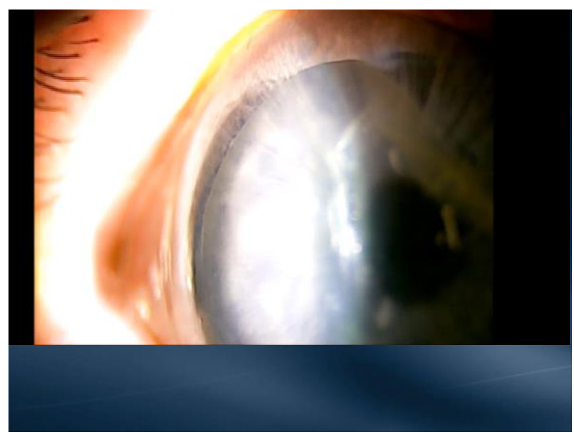
KeratoConjunctivitis Sicca

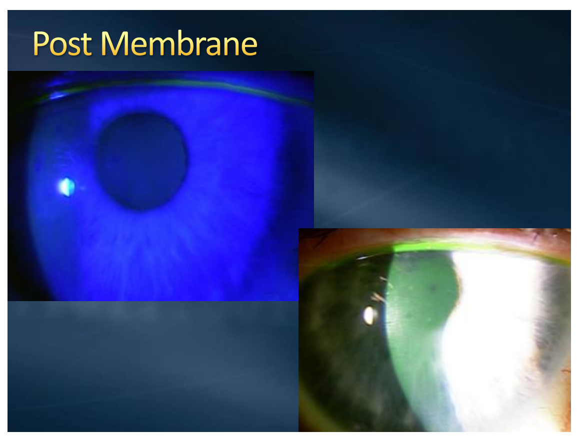
- Clinical findings
  - Tear film instability
  - Ocular inflammation
  - Pro-inflammatory cytokines are upregulated
  - Elevated levels of MMP noted
- Sutureless amniotic membranes contain anti-inflammatory mediators, growth factors and cytokines
  - Help restore a healthy and non-inflamed ocular surface
  - Maintain a stable tear film

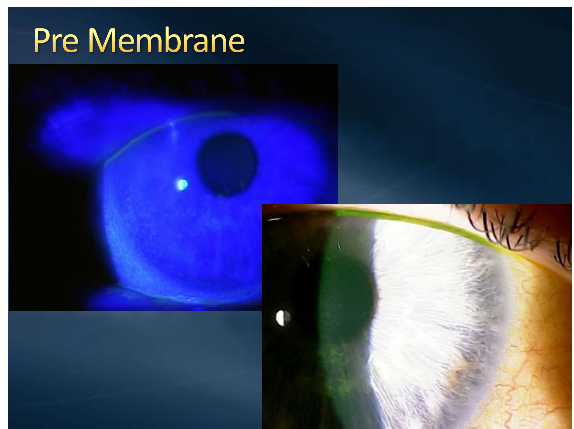
- Dryness is inflammatory condition
  - AM is potent anti-inflammatory
- Great induction therapy that takes the place of corticosteroid to be used in addition to other therapies
  - Restasis
  - Autologous Serum
  - DCN

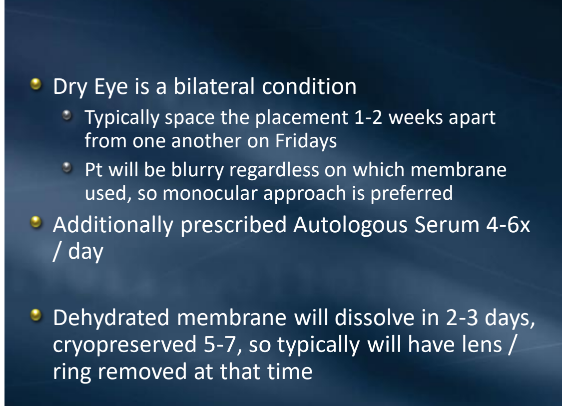
- 64yo Caucasian female
- Initially Referred in for Sjögren's syndrome dry eye, previously tried everything under the sun
- Rated dryness irritation 9/10
- Would like to try something different that gives long lasting relief






Post Membrane


Pre Membrane


Dry Eye is a bilateral condition
Typically space the placement 1-2 weeks apart from one another on Fridays
Pt will be blurry regardless on which membrane used, so monocular approach is preferred
Additionally prescribed Autologous Serum 4-6x / day
Dehydrated membrane will dissolve in 2-3 days, cryopreserved 5-7, so typically will have lens / ring removed at that time

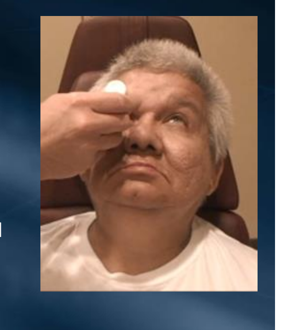
Bell's Palsy
G51.0

Bell's Palsy

- CN VII / Facial Nerve Palsy
- Can compromise the cornea in the setting of inadequate blinking and malpositioning of the midface and eyelid
- Facial nerve palsy can arise from a multitude of causes, although most cases are idiopathic
- Viral?
- A variety of non-surgical treatment modalities, ranging from scleral contact lenses to systemic steroids, have been explored and described in the literature

Bell's Palsy

- 58 year old white male presents with complaint of burning, tearing, and irritation x 1 month
- Patient reports issues with incomplete blink OD and trouble with drooping facial features on right side.
- Diagnosis of Bell's palsy made.

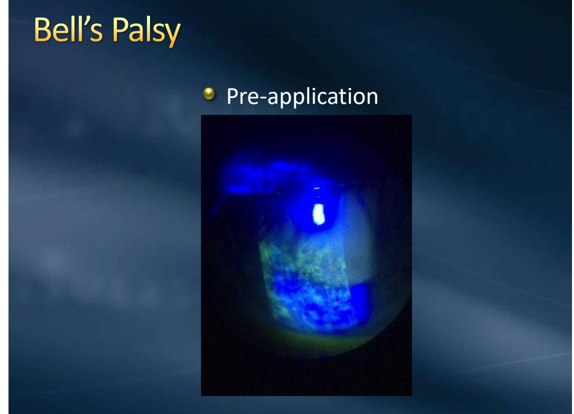


Bell's Palsy

- BCVA 20/50 OD and 20/20 OS
- Slit lamp exam shows significant SPK OD with incomplete blink
- Patient opted for sutureless amniotic membrane. Patient returned in 3 days for application.

Bell's Palsy

- Pre-application

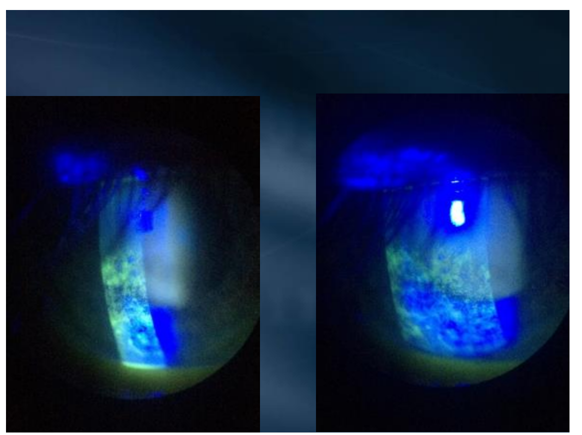


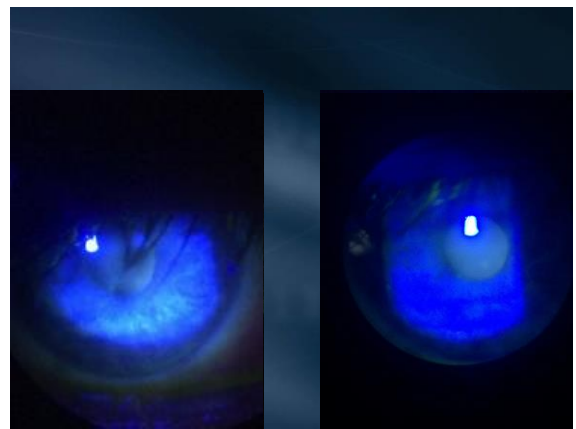
Going home instructions

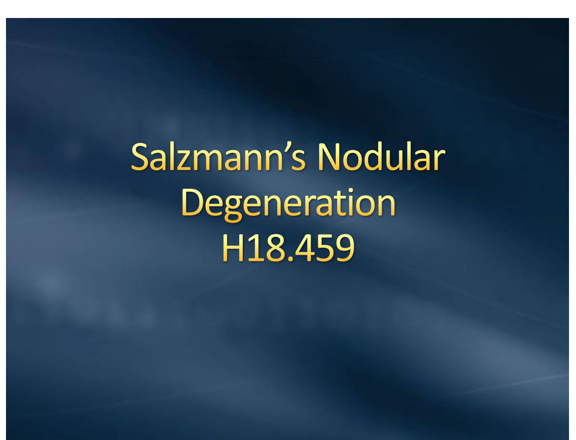
- Vigamox BID OD
- Alrex ophthalmic suspension BID OD
- Due to incomplete blink, patient was asked to use a small piece of tape to create partial temporary tarsorrhaphy to hold AM and BCL in place.
- Patient instructed to return in 2-3 days

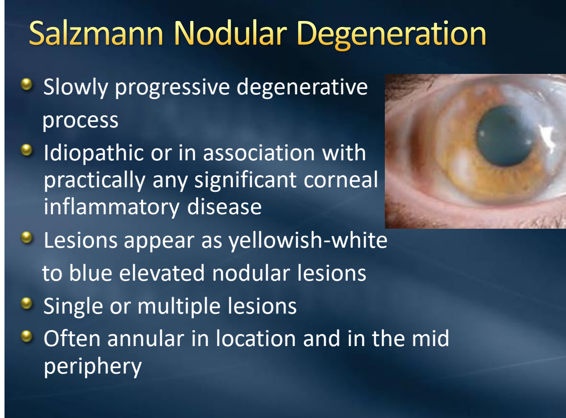
Bell's Palsy
Patient returns in 5 days
Reports better comfort and vision OD day prior
Thinks he may have rubbed CL out night prior

Bell's Palsy
Post-application
BCVA 20/20 OD, OS
Better comfort
Continue Alrex, add tears






Salzmann's Nodular Degeneration
H18.459

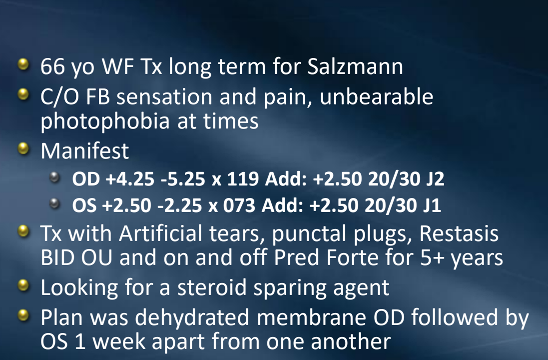

Salzmann Nodular Degeneration
Slowly progressive degenerative process
Idiopathic or in association with practically any significant corneal inflammatory disease
Lesions appear as yellowish-white to blue elevated nodular lesions
Single or multiple lesions
Often annular in location and in the mid periphery

Salzmann Nodular Degeneration

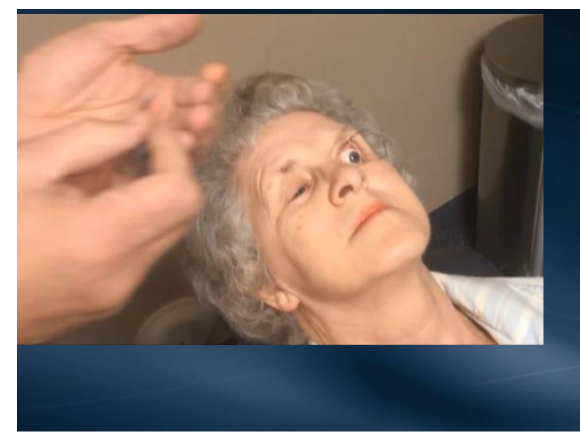
- Seen adjacent to corneal scarring or corneal pannus
- Iron line at the edge of the nodules common
- Found more often in women than in men and may be either unilateral or bilateral
- Patients asymptomatic or have decreased acuity, glare, FB sensation, pain, photophobia or tearing

Salzmann Nodular Degeneration

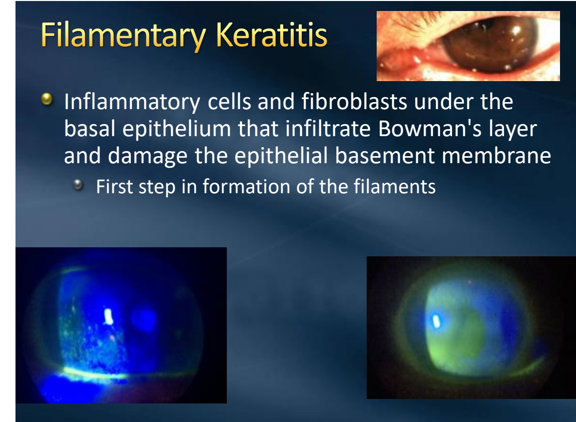
- Exact cause still undetermined
  - Associated with previous inflammation of ocular surface
    - Keratitis
    - Dry eye
    - Pterygium
    - Long term CL wear
  - Stone et al demonstrated increased expression of MMP-2
- Large majority of patients have MGD, DES, previous CL wear
  - suggesting chronic ocular surface inflammation is part of the cause
  - Tx consists at targeted med therapy



- 66 yo WF Tx long term for Salzmann
- C/O FB sensation and pain, unbearable photophobia at times
- Manifest
  - **OD +4.25 -5.25 x 119 Add: +2.50 20/30 J2**
  - **OS +2.50 -2.25 x 073 Add: +2.50 20/30 J1**
- Tx with Artificial tears, punctal plugs, Restasis BID OU and on and off Pred Forte for 5+ years
- Looking for a steroid sparing agent
- Plan was dehydrated membrane OD followed by OS 1 week apart from one another
  - Ramp up steroid in anticipation



Honorable Mention Indications



Filamentary Keratitis

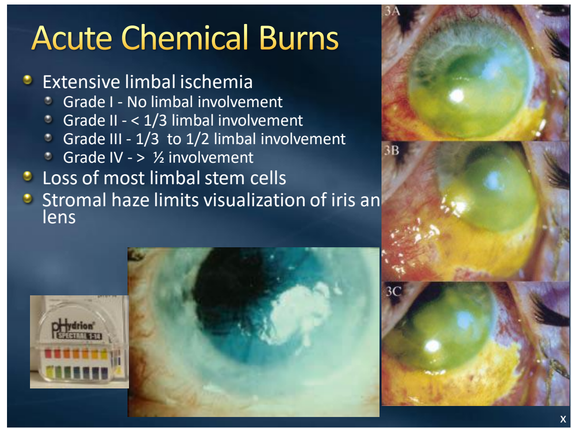
- Inflammatory cells and fibroblasts under the basal epithelium that infiltrate Bowman's layer and damage the epithelial basement membrane
  - First step in formation of the filaments

Microbial Keratitis

- Amniotic membrane for microbial keratitis
  - Promote healing, reduce haze/scarring
- Supportive studies
  - *Effect of amniotic membrane transplantation on the healing of bacterial keratitis.*
    - Invest Ophthalmol Vis Sci. 2008 Jan;49(1):163-7.
    - 3 treatment groups
      - Cefazolin and AMT
      - Non-preserved saline and AMT
      - Cefazolin without AMT
    - Best outcomes were with cefazolin and AMT group
      - Less haze
      - Less neovasculaization

Acute Chemical Burns

- Extensive limbal ischemia
  - Grade I - No limbal involvement
  - Grade II - < 1/3 limbal involvement
  - Grade III - 1/3 to 1/2 limbal involvement
  - Grade IV - > ½ involvement
- Loss of most limbal stem cells
- Stromal haze limits visualization of iris an lens



Acute Chemical Burns

- Two waves of intense inflammation
- First Wave occurs 12-24 hours after chem injury with infiltration of peripheral cornea with PMN and mononuclear leukocytes.
- Resulting from:
  - Blood elements from injured vessels in conj and uvea
  - Necrotic tissue of bulbar and tarsal conj
  - Chemotactically attracted byproducts of epi and stromal tissue
- Second, more aggressive wave of inflammatory cell infiltration begins at 7 days and peaks when corneal repair and degradation are maximal (bet 14-21 day)

Acute Chemical Burn

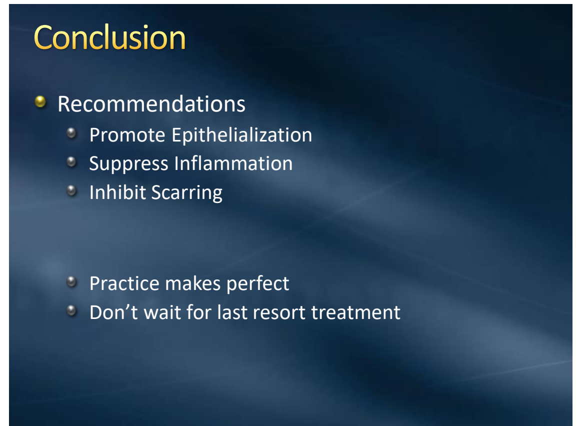
- Medical Management
  - Amniotic Membrane by day 3
  - Topical Pred Forte Q1h or Durezol Q2h x 7 d then taper & switch to
    - 1% topical medroxyprogesterone QID
  - 1% Atropine QD
  - Zymaxid / Moxeza / Besivance QID
  - Non Preserved artificial tears q1h
  - 100mg Doxycycline BID PO
  - 500 mg Diamox BID PO
  - Ultram 100mg PO q4-6h
  - Topical 10% ascorbate and 10% Citrate Q2h

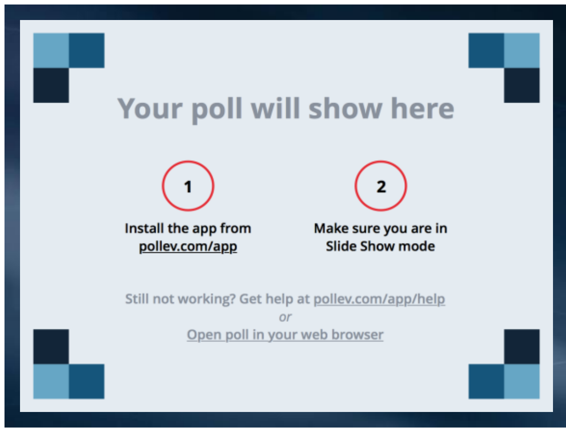
Future Consideration

- Biologic Therapies are continuing to expand
  - Over 900 studies being performed for Biologic therapies
  - Anticipate increased utilization over next 5 years
  - Amniotic Gel / Ointment
  - Amniotic Drops

Conclusion

- Use of sutureless amniotic membranes has shown to provide valuable tool to control inflammation and promote epithelialization
- Indications for use are increasing and recommending considering its usage earlier in the treatment paradigm


Conclusion
Recommendations
Promote Epithelialization
Suppress Inflammation
Inhibit Scarring
Practice makes perfect
Don't wait for last resort treatment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