# Amniotic Membranes In Primary Eye Care

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## Peter J. Cass, OD - Disclosures

- Vice President, Practice Compliance Solutions
- Past President, Texas Optometric Association
  - Chair HIT Committee, member AOA HIE Workgroup
  - L&L Committee, Third party Committee
- Adjunct Faculty, University of Houston College of Optometry
- Board Member, Elevate Digital Optics Lab
- Associate, MyEyeDr Beaumont
- Consultant/Speaker for ophthalmic companies:
  - Alcon, Bausch & Lomb, BioD, Crystal Practice Management, Diopsys, Solution Reach, Katena, Tear Science, Shire, Weave
- Lecturer for
  - Professional groups: Vision Source, Vision West, ECPN, PERC, Vision Trends, Vision West, TSO, etc.
  - Universities: RSO, UHCO, UAB, etc.
  - State associations: TOA, and over 20 others
- Working relationships with: CodeSafePlus, Clienman, Power Practice
- Shareholder Essentia, EDO labs, PCS, CVS

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## Types of Disks Available

Cryopreserved

Dehydrated


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## Cryopreserved Overview

- Sizes
  - Inner diameter of 16mm
  - Outer diameter of 21 mm
  - Clipped to a **dual polycarbonate ring** system
- **10 minute Office Procedure**
- Must be stored at **freezing** temperature
- Can last up to **1 year**

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## Dehydrated Overview

- Single layer of AM
  - 40 microns thick (nominal)
  - Sizes: 9mm/12mm/15mm
- With chorion layer
  - 100 microns thick (nominal)
  - Sizes: 15mm
- **Fixated with BCL**
- 10-minute Office Procedure
- Can be stored in **exam room drawer**
- Can last up to **5 years**


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## Clinical Use

- Cryopreserved
  - Over 90,000 grafts in eyes
  - Over 300 published reports

- Dehydrated
  - Since 2007
  - Over 70,000 grafts in eyes
  - Over 250,000 grafts in all


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## Amniotic Drops?

- Makers of the drops claim they can treat eye conditions, namely dry eyes and inflammation.
- But there are no FDA approved drops. In fact, the FDA sent warning letters to 2 companies in 2022.
- Regener-Eyes and M2 Biologics, were illegally selling unapproved eye drops


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## Amniotic Drops

- Probably not effective.
- Yes, some researchers have touted the potential regenerative and healing properties of amniotic fluid for eye conditions.
- And we have good results with amniotic *membranes*, but
- To date, only one clinical trial of amniotic fluid eye drops has been published
  - ➢randomized, controlled trial involving 61 people found that amniotic fluid was no better than placebo

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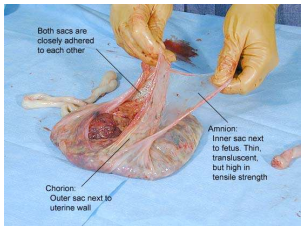
## What is Human Amniotic Membrane?

- A unique, avascular membrane separating the mother from fetus
  - **inner lining of placenta**
- Provides an incubating environment
  - **promoting cellular differentiation**
- Provides an immunological barrier
  - **prevents "foreign body" rejection**

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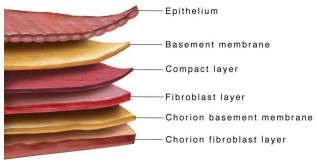
## Unique Grafting Characteristics

- Facilitates **epithelial cell migration**,
- Reinforces **adhesion of basal cells**,
- Promotes **epithelial differentiation**
- **Prevents** epithelial **apoptosis**.
- Can act as a bandage contact lens
  - Reduces pain
- Widely used since early 1990s
  - anti-inflammatory,
  - anti-fibrotic,
  - anti-vascularization
  - anti-scarring effects

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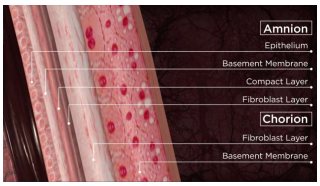
## Amniotic Membrane - Profile




- Contains:
  - Structural proteins
  - Specialized proteins
  - **Cytokines**
  - **Growth Factors**

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## Structural Proteins

- aka Extracellular Matrix
  - a structured substance produced by cellular activity
  - lies within the tissue, outside the cell
- **Collagens** Types I, III, IV, V, VII
- **Specialized proteins**
  - Elastin,
  - Fibronectin,
  - Laminin
  - proteoglycans, and
  - glycosaminoglycans


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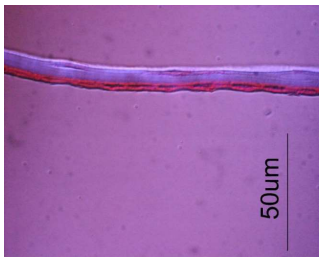
## Specialized Proteins / Cytokines

- Cytokines
  - large category including chemicals & proteins
  - Aid in **maintaining corneal clarity**
- Interleukin 4, 10
  - Responsible for **inflammatory response and control**
- Tissue Inhibitors to Metalloproteinases (TIMPS) 1,2,4
  - **Suppress MMP**

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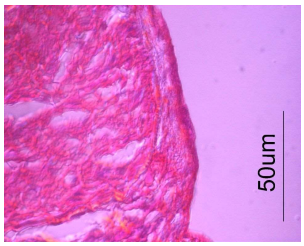
## Growth Factors

- A subset of cytokines
  - proteins responsible for eliciting a cell response and cell-to-cell communication
- Includes
  - Fibroblast **Growth Factor** (FGF)
  - Transforming **Growth Factor** Beta (TFG-β)
  - Epidermal **Growth Factor** (EGF)
  - Platelet-derived **Growth Factor** (PDGF A&B)
- **Promotes and accelerates epithelialization**

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## How it works – Key Points

- Cytokines
  - Cell signaling molecules that aid cell to cell communication in immune responses and **stimulate the movement of cells towards sites of inflammation**, infection and trauma
- Growth Factors
  - Proteins that bind to receptors on the cell surface, with the primary result of **activating cellular proliferation and/or differentiation**

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## Screening

**Donor**
- ✓Infectious,
- ✓Malignant,
- ✓Neurological
- ✓Auto-immune
- ✓and other exposures or social habits

**Blood**
- ✓HIV-1 & HIV-2 Antibody
- ✓HIV-1 (RNA-NAT)
- ✓Hepatitis B Surface Antigen (HBsAg)
- ✓Hepatitis B Core Antibody (HBcAb)
- ✓Hepatitis B Virus (HBV, DNA-NAT)
- ✓Hepatitis C Antibody (HCVAb)
- ✓Hepatitis C Virus (HCV, RNA-NAT)
- ✓Syphilis (RPR)
- ✓HTLV I & II Antibody (HTLV I/II Ab)

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## Processing

- Aseptically processed according to current:
  - **Good Tissue Practices** (cGTP)
  - **Good Manufacturing Practices** (cGMP)
- **Cryopreserved**
- Stored in validated medium of **Dulbecco's Modified Eagle Medium**/Glycerol (1:1)
  - Containing Ciprofloxacin and Amphotericin B.
  - Class II medical device
  - 1 year shelf life in freezer

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## Dehydrated Screening

**Donor**
- ✓ Screened by Surgical Biologics medical director
- ✓ Pathologist certified by the American Board of Pathology in
  - clinical pathology
  - blood banking/transfusion medicine

**Blood**
- ✓ HIV-1 & HIV-2 Antibody
- ✓ HIV-1 (RNA-NAT)
- ✓ Hepatitis B Surface Antigen (HBsAg)
- ✓ Hepatitis B Core Antibody (HBcAb)
- ✓ CMV Total Antibody
- ✓ Hepatitis C Antibody (HCVAb)
- ✓ Hepatitis C Virus (HCV, RNA-NAT)
- ✓ Syphilis (RPR)
- ✓ HTLV I & II Antibody (HTLV I/II Ab)

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## Dehydrated Processing

- Serological testing
  - per FDA and AATB
- Placenta is recovered in OR environment
  - Immediately following child delivery
  - Placed sterile container w/ hypertonic solution
- Transferred to Class 100 bio safety cabinet
  - Gentle washes and sterile water rinses to remove unwanted biological material
- Tissue stabilization
  - accomplished by dehydration
- Packaged in inner & outer peel pouch system
  - then dosed with Electron-Beam irradiation
  - terminal sterility > 5 year shelf life

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## DryFlex Processing

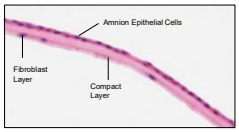
Retains the structure of unprocessed human amniotic membrane including extracellular matrix (ECM)

- Laboratory analyses and assays demonstrated that DryFlex® processing preserves continuous, intact epithelium, basement membrane, compact and fibroblast layers of the amniotic tissue, as illustrated in the histology section on the right. Other histological assessments demonstrated the presence of collagen and proteoglycans.

Retains key proteins of unprocessed human amniotic membrane

- Laboratory analyses and assays demonstrated that the presence of cytokines and growth factors were maintained with particularly high quantities of EGF, PDGF, TGF-ß, and TIMPs 1 and 2.

Histology of BioDOptix
(Magnified image of BioDOptix Amniotic Extracellular Matrix)




Hematoxylin and Eosin (H&E) stained tissue demonstrating normal amnion architecture with intact epithelium, compact layer and fibroblast layer.

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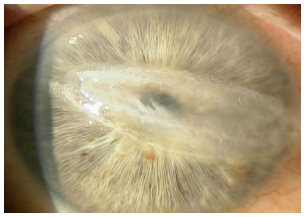
## Indications: Diseases with Pre-existing Epithelial Defects

- To promote wound healing and reduce complications (debridement is optional)
- Neurotrophic Persistent Corneal Epithelial Defect
- Post-Infectious Recalcitrant Corneal Ulcers (e.g. herpetic, vernal, and bacterial)
- Non-Healing Epithelial Defect After PRK/PTK
- Acute Chemical / Thermal Burns
- Acute Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis



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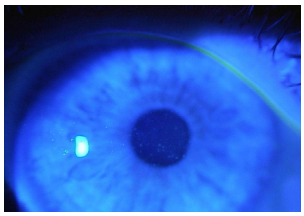
## Indications: Diseases without Epithelial Defects

- To prevent further damage and promote regeneration (no debridement/PTK)
- **Dry Eye Syndrome**
- **Superficial (Punctate) Keratitis**
- **Filamentary Keratitis**
- Radiation Keratitis; whorl pattern indicative of limbal stem cell injury
- Exposure (Graves) Keratopathy



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## Indications: Diseases w/ Unhealthy Epithelium or Basement Membrane

- To promote regeneration (after debridement / PTK)
- **Recurrent Corneal Erosion**
- Salzmann's Nodular Degeneration
- Bullous Keratopathy during/following DSEK
- Haze after PTK
- Partial Limbal Stem Cell Deficiency
- **Corneal Dystrophy** (e.g., Reiss Buckler)

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## When to use amniotic membranes?

- Virtually any **corneal or conjunctival** surface disease that involves **inflammation** may benefit from the use of an amniotic membrane
- The literature supports favorable outcomes in almost every aspect of inflammatory or infectious keratitis
- In most patients and most conditions, **early placement** of an amniotic membrane is generally more favorable to the healing of the ocular surface

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## Treatment Guidelines

- **Complete success** of an amniotic membrane placement procedure is defined as complete healing of the ocular surface after **one application** of the allograft without further intervention
- **Partial success** is partial healing of the ocular surface **requiring further intervention**
  - Bandage contact lens treatment
  - Repeat amniotic membrane placement
  - Topical medical therapy
- **Failure** is defined as lack of documented improvement with amniotic membrane therapy or discontinuation of the therapy session prior to demonstrable improvement

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## Treatment Protocol

- Perform the placement procedure early in the day if possible
- **Telephone follow-up** or in-office examination 4-6 hours later
  - No hyper-lacrimation
  - No foreign body sensation
  - No conjunctival hyperemia
  - No ocular pain
- **1-day postoperative** examination the next day
- **Daily postoperative examinations** until the amniotic membrane is absorbed and cannot be visualized
- If the allograft is still present after four days, terminate the therapy session

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**Cryopreserved Insertion Technique**

1. Apply anesthetic

2. Hold upper eyelid

3. Have patient look down

4. Insert into superior fornix

5. Pull lower lid down and slide under

6. Check centration with microscope

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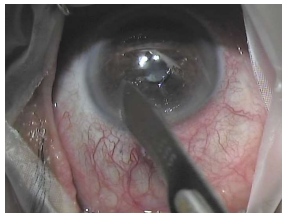
## Step 1: Prep and Denude

- Patient in supine position
- **Spec the eyelids**
- Apply topical anesthesia
- **Denude** 1-2 mm of epithelium surrounding defect with gentle blade or wek cell



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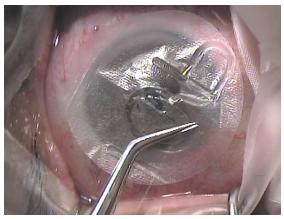
## Step 2: Placement of Dehydrated

- Maintain **dry ocular surface**
- Center graft on cornea
- Place **dull side down**
- Gently smooth using traction, counter traction
- 1-2 mm over peripheral conj
- **Disregard small creases and bubbles**



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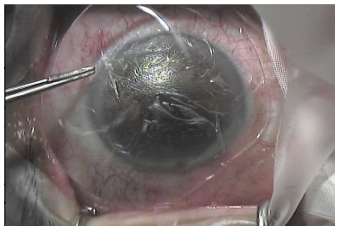
## Step 3: Placement of Lens

- 18, 16 or 14mm BCL
- Non tooth forceps
- **Center lens over Dehydrated**
- Maintain centration of disk over cornea



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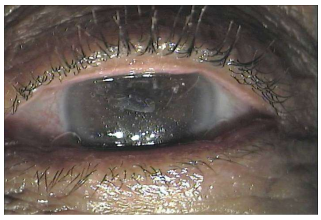
## Step 4: Finish

- Gently remove speculum
- **Request several blinks**
- Disregard small bubbles, creases
- **Apply appropriate meds**

- < 10 minute procedure



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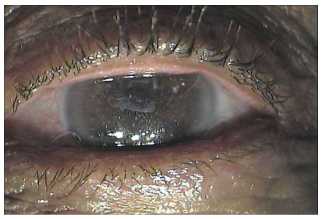
## Can do without Speculum too

- Have staff hold lid open
- No chances of scratching eye with speculum



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## Alternate Step 1: Prep and Denude

- Patient seated
- Apply topical anesthesia
- **Denude** 1-2 mm of epithelium surrounding defect with **wek sponge**

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## Alternate Step 2: Placement of Dehydrated

- Dry back surface of CL
- Center graft on CL
- Place **dull side up**
- Gently smooth
- **Disregard small creases and bubbles**

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## Alternate Step 3: Placement of Lens

- 18, 16 or 14mm BCL
- Insert CL w/ Dehydrated
- Maintain centration over cornea

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## Alternate Step 4: Finish

- Request several blinks
- Disregard small bubbles, creases
- Apply appropriate meds

- < 10 minute procedure

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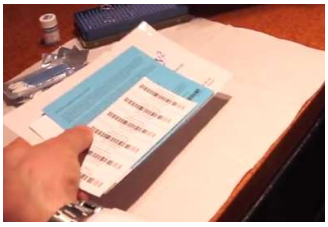
## Additional steps

- Fill out paperwork



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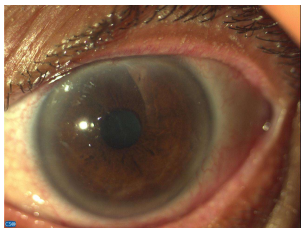
## Dehydrated: Management

- Follow up: 48 hours
- Dehydrated dissolves during healing
- Absorption: 7-14 days
- Rx: Doctor discretion, judgment



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### Cryopreserved Removal Technique

1. Apply anesthetic

2. Pull lower lid down

3. Lift lower edge

4. Ask patient to look down

5. Apply gentle pressure on upper lid

6. Slide out

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## Use in Dry Eye Syndrome

- Dry eye syndrome evolves through a sequence of four milestones:
  1. **Loss of water from the tear film w/ increase in osmolarity**
  2. **Increased conjunctival epithelial desquamation**
  3. **Increased corneal epithelial desquamation**
  4. **Destabilization of the cornea-tear interface**

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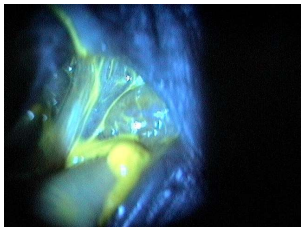
## Loss of Water from the Tear Film

- Loss of water from the precorneal tear film results in **decreased tear film volume** and is associated with debris in the tear film
- **Dehydrated mucus** that has precipitated in the inferior fornix indicates severe loss of water from the tear film



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## Conjunctival Epithelial Desquamation

- Abnormal increase in **conjunctival epithelial sloughing** results in immature conjunctival epithelial cells moving onto the surface of the eye
- As the desquamation accelerates, the **damaged cells release inflammatory mediators** onto the surface of the eye and the inflammatory process begins

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## Corneal Epithelial Desquamation

- Continued exposure to the osmotic gradient produced by **high tear film osmolarity** will eventually damage the cornea
- As cornel desquamation accelerates, the damaged cells perpetuate the inflammatory process by **releasing inflammatory mediators** onto the ocular surface

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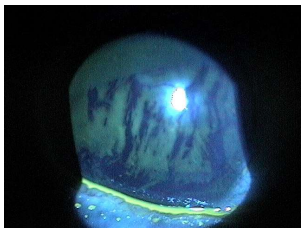
## Destabilization of Cornea-Tear Interface

- Abnormal tear film break-up time indicates tear film instability secondary to **loss of epithelial microvilli**
- The corneal epithelial changes required to cause tear film instability occur late in the natural history of dry eye syndrome



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## Many Other Uses

**Lets look at some case studies from my own patients…**

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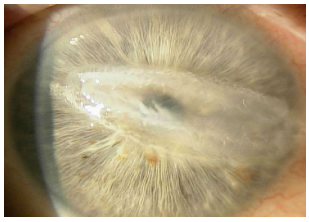
### Clinical Case: Thermal Burn

**Presentation**

- 68 YO WM
- Hit in eye with hot welding rod
- Severe lineal thermal burn over central corneal



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### Clinical Case: Thermal Burn

**24 hours later**

- Membrane in place
- Significant healing
- Patient pain free

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### Clinical Case: Thermal Burn

**5 day follow up**

- Membrane removed
- Wound completely resolved
- Minimal haze and scaring
- 20/25 uncorrected

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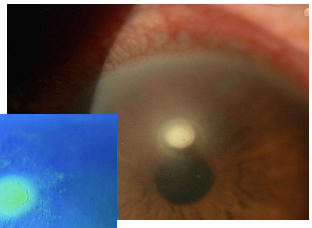
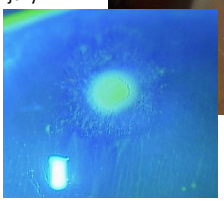
## Clinical Case: Corneal Ulcer

**Presentation**

- 54 YO HM w/ Severe corneal ulcer
- infection after work injury





- Hypopion
- Stromal haze
- Large defect
- Heavy staining

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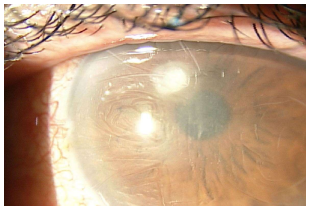
## Clinical Case: Corneal Ulcer

**2 day follow up**

- Membrane in place
- Haze clearing
- Vision normalizing



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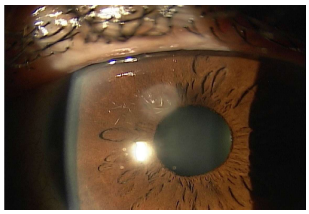
## Clinical Case: Corneal Ulcer

**20 day follow up**

- Membrane removed day 5
- Haze cleared
- Vision normal



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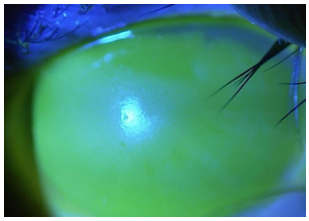
### Clinical Case: Alkali Burn

**Presentation**

- 48 YO HM
- Using a pressure washer to clean a building
- Severe alkali burn
- Affecting 99% of cornea



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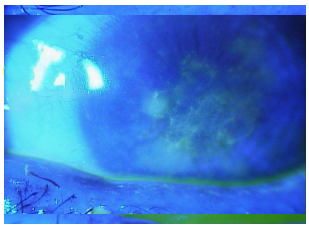
### Clinical Case: Alkali Burn

**11 day follow up**

- Almost re-epithelialized
- Small piece of membrane visible upon removal of bandage lens
- Rinsed well
- Mild edema and swelling
- Minimal pain
- Near normal vision



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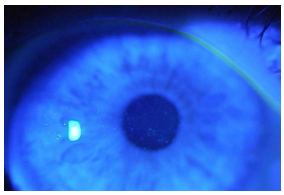
### Clinical Case: Alkali Burn

**28 day follow up**

- Nearly resolved
- Minimal SPK
- 20/30 uncorrected acuity



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### Clinical Case: HSVK

**Presentation**

- 65 YO WF
- Herpes simplex keratitis
- Recurrent, non healing
- Vascularization inf/temp

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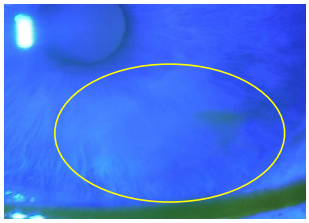
### Clinical Case: HSVK

**7 day follow up**

- Membrane dissolved
- Epithelial defect gone
- Vascularization mostly gone



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## Potential Complications

- **Patient intolerance**
  - Cryopreserved allograft (10% - 50%)
- **Poor surgical technique**
  - Allograft instability
  - Dislodged allograft
  - Superficial corneal lacerations
- **Poor cornea-contact lens relationship**
  - Red eye secondary to overnight contact lens wear
- **Rejection of transplant tissue**
  - A type II allergic reaction
  - Cytotoxic hypersensitivity

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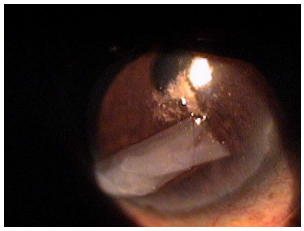
## Dislodged Allograft

- Clinical appearance at follow-up examination
- Chronic **foreign body sensation**
- **Mild ocular discomfort**
- Treatment is to **discontinue** the amniotic membrane therapy



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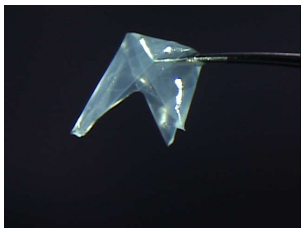
## Dislodged Allograft

- Most common cause of allograft instability is **poor application technique**
- Second most common cause is **aggressive eye-rubbing** by the patient during the therapy period



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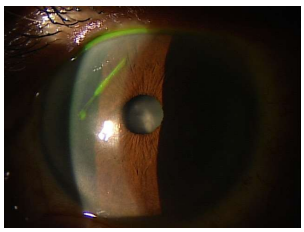
## Superficial Corneal Laceration

- **Superficial corneal injury** associated with a less than ideal (i.e., wrinkled) dehydrated amniotic membrane allograft placement
- Onset of **moderate ocular discomfort** is **4-6 hours after** placement procedure
- Best treatment option is to **discontinue** dehydrated amniotic membrane therapy



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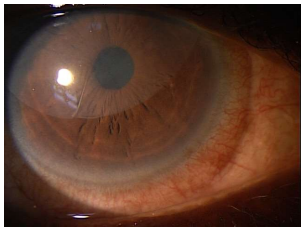
## Poor Cornea-Contact Lens Relationship

- Cornea-contact lens relationship results in a **"tight" lens fit** peripherally
- **Base curve that is too steep** allows for superior allograft migration
- Treatment **options**
  1. discontinue AM therapy
  2. Try again with different CL



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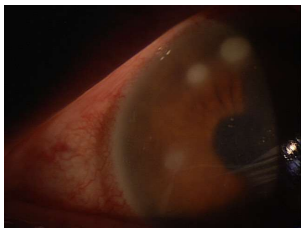
## Rejection of Transplant Tissue

- Moderately-severe to severe **pain**
- Conjunctival **hyperemia**
- Loss of corneal stromal transparency **decreases vision**
- **Eyelid edema**
- Multiple, **greyish-white large mid-peripheral corneal infiltrates**
- **Elevated IOP**
- Onset **2-12 hours after placement** procedure



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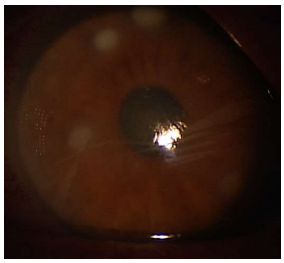
## Cytotoxic Hypersensitivity

- A **type II allergic reaction** that involves the interaction of immunoglobulins with foreign or autoantigens closely associated with cell membranes
- In this condition, the antigen is the amniotic membrane allograft
- **Allograft is recognized as foreign** and IgG or IgM antibodies are formed which react with and activate the serum complement enzymatic cascade
- **Corneal stromal cell lysis may result** from complement activation and from recruitment of leukocytes



Allergic reaction 48-hours after exposure

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**Coding and Billing**

**ICD**

- Many allowable ICD codes

**CPT**

- 65778… Placement of amniotic membrane on the ocular surface for wound healing, self retaining

**Medicare allowable**

- **$1265.80**

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## Drops

- Drops are not membranes
- You cannot apply drops and bill for a membrane

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## Questions?

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