Sutureless Amniotic Membranes 2.0:
2017 and Beyond
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COA Monterey Symposium 2017

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Disclosures

- Allergan Pharmaceuticals Speaker’s Bureau
- Bio-Tissue
- BioDLogics, LLC
- Katena/IOP
- Seed Biotech
- Johnson and Johnson Vision Care, Inc.
- Shire Pharmaceuticals

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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.

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
- Rheumatoid Arthritis
- Enbrel
- Remicade
- Humira
- Macular Degeneration
- Macugen
- Avastin
- Lucentis
- Eylea

What is the Amniotic membrane?
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.
- Anti-Inflammatory
- Anti-scarring
- 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

Available Sutureless Membranes

<table>
<thead>
<tr>
<th>Membrane Type</th>
<th>Contact Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>ProKera®</td>
<td>1-888-206-8813, 7030 SW 97th Avenue, Suite 211, Miami, FL 33173, <a href="http://www.prokera.com">www.prokera.com</a></td>
</tr>
<tr>
<td>Ambio-Disk</td>
<td>3374 K Avenue, Costa Mesa, CA 92626, 949-549-1185, <a href="http://www.ambiodisk.com">www.ambiodisk.com</a></td>
</tr>
</tbody>
</table>

Orthopedic / Podiatric

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

Studies on the Science
Cryopreserved Amniotic Membranes

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
All stored at room temperature
Shelf life typically 2-5 years
Do not need to be rehydrated
All require the use of BCL

AmbioDisk (IOP Inc. / Katena)
BioDOptix (BioDLogics)
Aril (Seed Biotech)
VisiDisc (Skye Biologics)
AlphaVision (Amniotic Therapies)
ReNovaAT (RegenMed)
AmnioTek-C (ISPP Surgical LLC)

Dehydrated Membranes

- Ambio Disk
  - Ambio 2 (35μ)
  - 9, 12 or 15 mm
  - Ambio 5 (100μ)
  - 15 mm
  - BCL of choice

- BioDOptix
  - Two Disc Sizes
    - 9 mm, 12mm or 15mm
  - BCL of choice
  - 40-60um thick membrane

- 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
  - 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

- Skye Biologics Thin (45μ)

- VisiDisc Thick (200μ)

- Renovo-AT
  - 9, 12, 15 mm discs

- AmnioTek-C

Dehydrated 4 Step Process

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

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

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
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

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 Erosions**

**Recurrent Corneal Erosion**

H18.839

**Courtesy of Ramamurthi et al**
Recurrent Corneal Erosions

- 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

- 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

Controlled Studies on RCE


Stepwise Approach

- Medical Management
  - Bandage CL
  - Epithelial debridement
  - Autologous Serum
  - Surgical Intervention

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

Dec 2013
- Corneal Debridement
- Start gatifloxacin QID
- Amniotic Membrane – Prokera Slim
- Inserted in office
- Corticosteroid for 8 weeks
  - Begin Pred Forte QID x 2 weeks, then BID x 6 weeks
- EW BSCL for 12 weeks
  - Apply after removal of ring, approx. 1 week

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

Day 21
- Swapped out BSCL with another
- Continue Pred Forte BID for 5 weeks
- Continue gatifloxacin QD prophylactic

Day 35, 49, 63, 77, 91
- Swapped out BSCL with another q2weeks
- Continue Pred until 8 weeks

Been symptom free and no recurrences since December 2013
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.

**Neurotrophic Keratitis**

**H16.239**

**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 mucous 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

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

**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

**Case Presentation**

**Patient returns in 4 days**
- Membrane dissolved
- BCL gone???
- Still using Besivance
- RTO in 3 days

**Post Day 16**
- Patient feels vision back to normal
- Discontinue drops

**Post Day 16**
- Patient returns in 2 days
- Vision seems slightly clearer
- Clinical appearance improved

**Plan**
- Continue Besivance QID OS
- RTO 3-4 days

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

**H04.129**

- 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

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**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
- 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
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.

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.

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

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

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’s 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
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.
    - 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 neovascularization
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 and 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

Recommendations

- Promote Epithelialization
- Suppress Inflammation
- Inhibit Scarring
- Practice makes perfect
- Don’t wait for last resort treatment
- Did wetlab/hands on workshop this morning
- Thanks to our wetlab donors
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