Recurrent Corneal Erosion Syndrome

- Relatively common condition
- Many cases have past Hx of trauma
- Corneal dystrophies

Management can be frustrating for both patient and doctor
- Patient discouraged because of recurrent pain and decreased vision
- Doctor disheartened by inability to cure disease

Recurrent Corneal Erosion Syndrome

- Recognized as a disease entity for over 100 years
  - First report published in 1872 by Hansen
    - “Intermittent neuralgic vesicular keratitis”
  - Von Arlt published same phenomenon 2 years later
  - 1900: Sill reported epithelial irregularities and gray dots associated with recurrent erosion
  - 1901: Stood suggested trauma to epithelium and anterior stroma resulted in an inability of new epithelium to form normal attachments to the injured anterior Bowman’s layer
  - 1921: Vogt described fine white dots on Bowman’s layer, NaFl staining, and an irregular epithelial surface with localized edema

Recurrent Corneal Erosion

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

Differential Diagnosis

- Self – inflicted corneal injury
- Exposure keratitis
- Recurrence of Herpes Simplex Keratitis
- Neurotrophic Keratitis
- Roughening of tarsal plate
- Foreign bodies under tarsal plate

Recurrent Corneal Erosion Syndrome

- Age range 24-73 years
  - Highest prevalence between third and fourth decades
  - In 5 studies the mean age was 38.42, 44.45, 43
  - Mean age 42.5
- Equal distribution between men and women (slight female)
- Interval between initial abrasion and first recurrence: 2 days to 16 years
- Family history in 3%
- 10% cases bilateral
- Pain is the most common symptom (followed by)
  - Watering
  - Blurred vision

The above slides provide information on recurrent corneal erosion syndrome, recurrent corneal erosion, and differential diagnosis. The slides discuss the characteristics, management, and historical context of recurrent corneal erosion.
Incidence of RCE 1:150 cases following a traumatic abrasion
Majority – 87% (one study) occur within the lower half of the cornea irrespective to the etiology
In close proximity to Hudson-Stahl line
Tiredness, menopause, menstruation, and alcohol were recognized as aggravating factors
Pts with EBMD who suffer trauma are more likely to suffer from RCE
Despite conservative Tx, 5% of cases continue to suffer recurring episodes

Reattachment of corneal epithelium following an abrasion appears faulty
Variety of adhesion complex defects have been observed
1. Reduplication of BM
2. Loculation of connective tissues
3. Absence of BM and hemidesmosomes

Pathological Anatomy

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

Corneal Epithelium
- 5-6 cell layers thick
- 50um thick
- stratified squamous to Basilar columnar cell
- Rapidly renewing tissue which loses its surface cells into tear film
- Turnover 4-6 days
- Maintains smoothness of optical surface
- Barrier against microorganisms
- Maintains deturgescence of stroma

Numerous hemidesmosomes are scattered on the basal side of the epithelial cells
Fine fibrils radiate from them into the BM to join the two together
When epithelial defect occurs fibronectin covers the stroma to help allow adjacent cells to slide over the denuded area
Those cells will proliferate to form overlying superficial cells
The basal cells will begin to form adhesion complexes with the BM

In vivo laser confocal microscopy
1. irregularity in the alignment of superficial epithelial cells
2. gaps in the epithelial cell layers
3. enlargement of the basal epithelial cells
4. the absence or a reduced number of subepithelial nerves
5. brightly reflective granular structures in the basal and wing cell layers of the epithelium and in Bowman’s layer
6. activated keratocytes in the shallow stroma
7. scattered fine particles in the shallow stroma
8. infiltration of inflammatory cells in the mid stroma
9. keratoprecipitates on the corneal endothelium

None of these findings were detected in the 30 normal eyes examined.
**Pathological Anatomy**

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

**Pathological Anatomy**

- 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
    - 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.

**Classification**

- Conditions associated with RCE can be classified as either primary or secondary depending on whether the BM complex abnormality is intrinsic or acquired.
- **Primary**
  - Intrinsic
  - Due to corneal dystrophies
    - ABMO
    - Reis-Buckler's
    - Lattice, Granular, Macular
  - Bilateral and symmetrical
  - Develop in multiple locations on cornea

**Classification**

- **Secondary**
  - Acquired / Extrinsic
    - Traumatic abrasion
      - Sudden, sharp
    - Tear film abnormalities
    - Eyelid pathologies
    - Dry eye
    - S/P LASIK
    - Salzmann's Nodular
    - BK
    - Following ulcers

**Inherited Recurrent Corneal Erosion Dystrophy**

- IC3D new classification in 2008
  - placed each of 25 known corneal dystrophies into 1 of 4 categories
- Epithelial recurrent erosion dystrophy (ERED)
- Franceschetti Corneal Dystrophy
  - Dominantly inherited RCE
  - Attacks of RCE early in life – 1st decade
  - Subepithelial opacities in adult life,
  - decreased frequency of recurrent erosion attacks
Divisions

- **Microform**
  - Duration of 30 minutes to several hours
  - Typically have intact epithelial surface
  - More frequent
  - Often associated with EBMD
  - Punctate epithelial erosions

- **Macroform**
  - May last for several days
  - Pain, photophobia
  - Typically traumatic in origin
  - Frank epithelial defects or large areas of edematous non-adherent epithelium

Diagnosis

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

Controlled Studies on RCE


Management Options

- **Medical** – (>95% successfully managed, 70% remaining symptom free × 1 yr, 40% 4 years)
  - Promoting epithelial regeneration
  - Patching (rare), bandage contact lenses
  - Antibiotics, cycloplegics, hyperosmotics, corticosteroids
  - Oral tetracyclines
- **Mechanical**
  - When medical management is not successful
  - Debridement
  - Anterior Stromal Puncture (ASP)
- **Surgical**
  - Photorheochemical keratectomy (PTK)
  - Diamond burr superficial keratectomy
  - Nd:YAG
  - Alcohol Delamination
**Medical Management**

- Patching vs. BCL
- Lubrication
- Cycloplegics
- Antibiotics
- Topical NSAIDs?
- Corticosteroids
- Hyperosmotics
- Oral tetracyclines

**Management**

- Bandage CL
  - Designed to relieve pain
  - Protect epithelium from eyelids
  - Options
    - Acuvue Oasys (Vistakon)
    - Air Optix Night and Day (Ciba Vision)
    - Purevision (Bausch and Lomb)
  - CPT Code 92071 (99070) —Fitting of a contact lens for treatment of ocular surface disease
    - Old Code 92070 used to include materials (CL)
    - Now its just fitting of lens and need to bill for CL separately
  - Other lens choices: scleral CL, collagen corneal CL

**Management**

- Bandage CL
  - Lens should be fitted fairly tight
  - Min of 6 weeks is needed to allow BM remodeling to return to normal
  - Six weeks continuous wear
  - Concerns?


  - 12 pts fit w EW BSCL x 3 mo
    - Replaced q2weeks
    - Prophylactic ofloxacin 2x d
    - All pts felt immed relief after BSCL insertion and during 3 mo period
    - 75% asymptomatic after 1 year

**Medical Management**

- Lubrication
  - Gels, drops, ointments
  - Reduces friction
  - Maximizes health of tear film
- Cycloplegics
  - Reduce secondary inflammation
  - Improve comfort
  - Homatropine 5% BID
- Antibiotics
  - Prophylaxis
  - Topical NSAIDs
  - Used for analgesia
- Corticosteroids

**Medical Management**

- Hyperosmotics
  - Produce an osmotic gradient
  - Promote epithelial adherence
  - Minimize epithelial edema
  - Occurs overnight when lids are closed

**Medical Management**

- Doxycycline
  - Inhibits MMP
  - Improves melobian gland dysfunction
  - Doxycycline shows 70% decrease in MMP activity in corneal cultures
  - No recurrences after 21.9mo follow up
  - Dosage may vary
    - Sub anti-microbial dose
    - 20 mg to 50 mg BID
    - Tx for min of two months following RCE
Azasite
- AzaSite qhs in all cases of RCE in the presence of lid disease
- shown to inhibit MMP-9 in epithelium and endothelium
- May be better tolerated than DCN
- Off label
- Cost is concern

Corticosteroids
- Research shows that corticosteroids inhibit MMP-9 and other enzymes that are known to cause epithelial breakdown specifically in RCE
- Lotemax qid x 2 weeks then bid x 6 weeks
  - Concern of long term Tx
  - Side Effects (check IOP within 1 month)


FreshKote
- Focus Laboratories
- 2.0% Polyvinyl pyrroldione
- 0.9% Polyvinyl alcohol (87% hydrolyzed)
- 1.8% Polyvinyl alcohol (99% hydrolyzed)

FreshKote
- Treats all 3 tear film layers
  - Lipid layer: Amisol
  - Aqueous layer
  - Mucin layer
- Has a high oncotic pressure
  - Re-establishes integrity of epithelium
  - Reduces microcystic edema
  - Prevents recurrent damage
- Safe for CL wearers
- Prescription only

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- Behind the Counter (BTC)

Restasis and Punctual Plugs
- Bernauer et al.
  .......Due to thinning of the tear film, the lids might have tight adherence to the surface of the cornea overnight leading to tearing of epithelium upon wakening
Autologous Serum
- Use first described in 1984 by Fox et al (for keratoconjunctivitis sicca)
- Unpreserved, non-antigenic
- Utilizes patient's own blood serum
- Blood is drawn and serum is spun down and mixed with artificial tears.
- Doesn't contain red blood cells and clot factors
- Replaces individualized antibodies

Study in 2010 – 33pt
- 6x/day for 3 mo's, followed by 4x/d for 3 mo
- Pts seen 1d, 3d, 1 week, qmo x 12, q 3mo
- 28pts (85%) no recurrence
  - 2.5 years
  - Recurrence rate of 15% over 30 mo period makes it viable option
- 85% success


- Costly - $150-300 time, 2-4x/year
- Inconvenient - Requires blood donation from patient
- Possible risk of infection

Diabetic Patients
- Maintain adequate blood sugar
  - Proper diabetic control is first priority
  - HgbA1C <7%
  - 10% lower than current
- Advanced Glycation End product - AGE Inhibitor ?
  - Benfotiamine
  - Synthetic Thiamine
  - Lipophilic analog of Vitamin B1

The Effects of Long-Term Oral Benfotiamine Supplementation on Peripheral Nerve Function and Inflammatory Markers in Patients With Type 1 Diabetes: A 24-month, double-blind, randomized, placebo-controlled trial. Diabetes Care. 2012 Mar 23

Mechanical and Surgical Management
- Epithelial Debridement
- Prokera Amniotic Ring
- Anterior Stromal Puncture
- Nd:YAG Puncture
- Phototherapeutic Keratectomy (PTK)
- Alcohol Delamination
- Superficial Keratectomy

Epithelial Debridement
- Use cotton swab, spatula, spud, or jewelers forceps
- Begin by softening epithelium by instilling topical anesthetic q 15-30 sec for 1-2 min
- Work toward the center of the cornea
- Avoid pulling up or out
- Try to keep straight, firm edges
- Key is to make sure to get Bowman’s smooth
- BCL, topical antibiotics, topical NSAIDs PRN
- Oral analgesics if needed
- CPT 65435 (Removal of corneal epithelium) $103.58
- ED success 65-82% (varies)
Sutureless Amniotic Membrane's

- Ambio-Disk
- Bio-D Optix

Sutureless Amniotic Membranes

- Innermost of 3 membranes forming the fetal membrane
- Avascular and acellular. It will facilitate epithelial healing
- Combined action helps stimulate epithelialization

- Easy to insert in the office, bedside
- Monitor healing by fluorescein and IOP by Tonopen™ without removal
- Does not interfere with antibiotic penetration

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**Sutureless Amniotic Membranes**

**Pathophysiology**
- Faulty BM with poor adhesion complexes
- Poor epithelization
- Increased MMP

**AM Mech of Action**
- Promotes Epithelialization
- Suppresses Inflammation
- Inhibits Scarring
- Inhibits Angiogenesis
- Neurotrophic Factors
- Anti-Microbial Agent

**Mech of Action**
- Facilitates healing in most defects within 5-10 days at which point the membrane in the device will naturally dissolve.
- 65778 (the CPT code) Avg reimbursement $1670.34

**Anterior Stromal Puncture**

- First described by Mclean, et al 1986
- 20-25 gauge disposable hypodermic needle
- Under slit lamp making multiple punctures through loose epithelium and Bowman’s membrane into ant half of stroma.
- Approx 15-25 punctures spaced 0.5mm apart
- Orient needle perpendicular to corneal plane
- Exert enough pressure to indent the cornea one quarter to one-third depth of A.C. (0.1mm adeq)

**Potential Side Effects**
- Corneal perforation
- Scarring due to deep penetration
- Best utilized for pts w periph etiology
- Microbial keratitis
- Anterior uveitis
- DLK in post-LASIK patients
- Sub epithelial fibrosis
  - following Bullous keratopathy
  - Delayed 1-2 years
  - Most likely pre-existing
  - Tx w Superficial Keratectomy to remove membrane

- CPT 65600 (multiple punctures of anterior cornea) $499.79
- ASP with Needle 60-88%

**Anterior Stromal Puncture**

- Believed that breaching of Bowman’s stimulates a more secure bonding of epi to the underlying BM, Bowman’s and stroma
- Following ASP
  - BSCL (2 weeks)
  - Fluoroquinolone AB
  - Steroid
  - Non presv Art tears

**ND:YAG Laser Puncture**

- Similar in concept to anterior stromal puncture
- Study by Katz et al retrospectively studied 8 patients with RCE treated with the Nd:YAG laser
  - used 0.4- to 0.5-mJ pulses applied to the region of Bowman’s layer through an intact epithelium
  - all 8 patients (11 eyes) had resolution of their symptoms after treatment w f/u 21.2

**Benefits**
- Shallow, reproducible, translucent

**Concerns**
- Needs epi off for full breach into stroma
Superficial Keratectomy

- Total superficial keratectomy w blade or diamond knife.
- Dystrophic epi and BM are peeled in one continuous sheet leaving undisturbed Bowman’s
  - SK with blade 67-82%
  - SK with Diamond burr 75-100%

Figure 1. (Hodkin) The end of the AES with the attached rotary brush held above a patient’s eye. During the procedure, the patient’s head is rotated slightly toward the operative eye and irrigation solution is dripped onto the cornea while the brush is maneuvered to debride the corneal surface.

88% success

New method of superficial keratectomy

Amoils Epithelial Scrubber
- Handle with battery operated motor
- Rotates a disposable, circular brush
- Originally designed to remove central epithelium prior to PRK
- Effective for treating recalcitrant RCE
- Applied for longer duration to central and peripheral cornea

Transepithelial PTK (t-PTK)

- Same as PTK, though excimer is used to remove epithelium
- Holzer et al showed 80% had no RCE for 6-20 months
- No statistical significant change in refraction
- Ardjomand et al modified epithelial removal
- Hinged at 12 o’clock

Higher success rate in secondary cases (trauma)
Can be combined with PRK in appropriate cases

Risks
- Post-operative haze
- Cost
- Potential for hyperopic shift
- Pain

PTK 46-100%

Quick, safe and economical
Performed in controlled setting
- Epithelium very sensitive to alcohol
- 20% ethanol for >30sec
- Splits epi from stroma at level of Lamina lucida (lv) and densa (stays)
- Proteinaceous or cellular debris is removed
- Collagen VII remains
- Allowing new anchoring fibril formation
**Alcohol Delamination**
- Absolute Ethyl Alcohol is diluted to 20% w sterile water in 1 ml syringe
- Circular well sufficient to encompass area of erosions
- Few drops of 20% alcohol are dropped in well and left in place for 30 sec
- Alcohol is then drained w surgical sponge
- Irrigate with BSS
- Dry surgical sponge then removes epi in single sheet
- BSCL

- 17 pts failed conservative tx
- 83% success first year

**Alternative Treatment Options**

**Alternative Options**
- Corneal Cautery
- Conjunctival Flaps

**Substance P-derived peptide**
- Sensory neurotransmitter released from the trigeminal nerve during healing
- Confocal microscopy showed alterations in corneal nerves similar to neurotrophic corneas
  - Authors had previous success tx neurotrophic
  - Promoted epithelial migration and healing

Case report of 1 pt (32yo female) who suffered trauma RCE
- Failed med management, BSCL and Autologous serum
  - Experienced 26 RCE episodes
  - eye drops 4x/d combining 250 μg/mL of substance P-derived peptide
  - with 1 μg/mL of insulin-like growth factor I

**Substance P-derived peptide**
- Resolution of defect noted in 11 days
  - Tx D/C after 2 mo’s
  - 11 months no recurrence

- More studies needed

**Botox**
- Limited data
- Patients with RCE may have absent or weak Bell’s phenomenon
- Injections to orbicularis
- Superior, both nasal and temporal
- Mechanism of improvement
  - Decreasing effect of orbicularis during REM sleep in patients with abnormal Bell’s phenomenon

[Image of Botox treatment]
**Umbilical Cord Serum**
- Umbilical cord blood was collected from mothers who underwent vaginal delivery or Cesarean delivery.
- Blood was collected from the umbilical vein after fetal delivery.
- A volume of 200 to 250 mL of umbilical cord blood was collected.

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

**N-Acetylcysteine**
- NAC is a derivative of cysteine.
  - Which inhibits collagenase irreversibly.
  - It is believed that NAC inhibits MMP-9 in a similar fashion.
- A study in 2012 showed that NAC reduces MMP-9 production in human corneal epithelial cells, and inhibits cell migration.
- Making it a viable therapeutic option for RCE.

**Obscure treatment?**
- Hypnosis:
  - Treatment and prevention of RCE.
  - 1 case study using hypnosis and suggestions.
  - Patient remained symptom free for 20 months.

**Stepwise Approach**
- Medical Management
  - Bandage CL
  - Epithelial debridement
  - Autologous Serum
  - Surgical Intervention.

- Medical Management
  - Bandage CL
  - Epithelial debridement
  - Autologous Serum
  - Surgical Intervention
Medical Combination Tx
- Muro ung qhs >>> FreshKote gtts TID >>> Lotemax qid x 2 weeks then bid x 6 weeks >>> AzaSite
- Muro ung qhs >>> FreshKote gtts TID >>> Lotemax qid x 2 weeks then bid x 6 weeks >>> DCN
- Muro ung hs >>> FreshKote gtts TID >>> Autologous Serum >>> DCN
- Lotemax >>> DCN

Mechanical Combination Tx
- Epi debridement >>> Amniotic Membrane >>> >>> Autologous Serum >>> DCN
- Epi Debridement >>> EW BSCL 12 weeks >>> DCN >>> Lotemax
- ASP >>> BSCL 12 weeks >>> DCN >>> Lotemax

Surgical Combination Tx
- When to refer???:
  - After repeated medical and mechanical management failure
- Alcohol Delamination >>> BSCL x 12 weeks >>> DCN >>> Lotemax
- SK >>> BSCL x 12 weeks >>> DCN >>> Lotemax, AzaSite

Audience Treatment Options

Oral and Topical Vitamin C
- Put on a SCL prior to Bed
- Faith Healing
- Breast Milk

Case Presentation
47 wmo, Don E
- OHx
  - EBMD OS-OD and Hx
  - Trauma OS with RCE 0S
- Ongoing RCE approx qom, but mild disturbance each morning x 2 years
- Had Debrided cornea 6 mo prior but still experiencing RCE
- MHx
  - Obstructive Sleep Apnea
  - HTN
  - Migraines

Ant stromal puncture
- BSCL x 3mo
- DCN 20 mg BID PO x 3 mo
- Lotemax QID for 2 weeks, BID for 4 weeks (6 wks total)
- No recurrences after 20 months

Case Presentation

87 yo WF – Betty V - with H/O RCE for 3+ years
- OChx: BRVO, Cat Sx, Fuchs
- OcTx: punctal plugs, Restasis, ointments, gels, tears, Steroid drops, BSCL
- MedHx: Kidney removed (one kidney), HTN, osteoarthritis, osteoporosis
- RTO C/O pain and discomfort with morning awakening. OS Terrible pain 7 out of 10 and photophobia
- Noted to have 2mm epi defect on inf nasal cornea OS. 2+ injection and tr cell in AC.
Summary

- Commonly encountered in optometric practices
- Pay close attention to type of RCE (Primary vs Secondary)
- Lots of options when treating RCE
  - Remember the anatomy
- Don’t give up hope
  - Always something different to try
- 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

Thank you

Please feel free to contact us:

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