How to take the “Recurrent” out of Recurrent Corneal Erosion Syndrome
Nicholas Colatrella, OD, FAAO, Dipl ABO, ABCMO
Jeffrey Varanelli, OD, FAAO, Dipl ABO

Disclosure Statement:
• Allergan Pharmaceuticals
• BioTissue
• IOP Ophthalmics

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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

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

Differential Diagnosis

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

Recall:
- 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: Szili 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 Syndrome**

- Age range 24-73 years
  - Highest prevalence bet third and fourth decades
  - In 5 studies the mean age was 38, 42, 44, 45, 43
  - Mean age 42.5
- Equal distribution bet men and women (slight female)
- Interval bet initial abrasion and first recurrence
  - 2 days to 16 years
- Family Hx in 3%
- 10% cases bilateral
- Pain is most common symptom (followed by)
  - Watering
  - Blurred vision

**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-Stahli 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

**Anatomy**

- 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

- 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

**Pathological Anatomy**

- Reattachment of corneal epithelium following an abrasion appears faulty
- Variety of adhesion complex defects have been observed
  - Reduplication of BM
  - Loculation of connective tissues
  - Absence of BM and hemidesmosomes
- Corneal Epithelium
  - develops pale, swollen basal cells
  - Pseudocystic collections of cellular and amorphous debris are found within the epi (due to aberrant BM)
  - Leads to elevation of epi and accumulation of underlying debris
  - And the further formation of abnormal BM cycle self-perpetuates
• 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

• Epi 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 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

Pathological Anatomy

• Diabetic patients
  
  RCE is thought to be more common
  Deposition of AGE’s
  Advanced Glycation End Products
  Glucose cement on hemidesmosomes that anchor the basal epithelium to Bowman’s
  Anchor points are less elastic
  More prone to sloughing

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
  Intrinsinc
  Due to corneal dystrophies
  ABMD
  Reis-Buckler’s
  Lattice, Granular, Macular
  Bilateral and symmetrical
  Develop in multiple locations on cornea

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

Plant leaf, mascara brush, keys, toys, tree branches
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


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

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

Diagnosis

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

Slit lamp
- Epithelial
  - Microcysts (dots)
  - Reduplication of basement membranes (maps)
  - Extensions of collagenous filaments (fingerprints)
  - Loosely adherent, elevated epithelium

History
- Previous trauma?

Other
- Pain, photophobia, tearing


**Management Options**
- **Medical** — (>95% successfully managed, 70% remaining symptom free x 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**
  - Phototherapeutic 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

**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**

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

- **Doxycycline**
  - Inhibits MMP
  - Improves meibomian 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**

- 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

**Focus Laboratories**

- 2.0% Polyvinyl pyrrolidone
- 0.9% Polyvinyl alcohol (87% hydrolyzed)
- 1.8% Polyvinyl alcohol (99% hydrolyzed)

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  - Behind the Counter (BTC)
Restasis and Punctal 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 patients 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

Autologous Serum

- When applied on RCE
  - Extra supply for necessary glucose, proteins and calcium for the epithelium to migrate rapidly
    - Speeding up first phase of wound healing
  - Vitamin A and fibronectin also help speed this up
  - Affects final phases of wound healing by supplying necessary extracellular matrix components
  - Supplies growth factors that activates keratocytes to produce extracellular matrix components

Diabetic Patients

- Maintain adequate blood sugar
  - Proper diabetic control is first priority
    - HgA1C <7%
    - 10% lower than current

Advanced Glycation End product - AGE Inhibitor?

- Benfotiamine
  - Synthetic Thamine
  - Lipophilic analog of Vitamin B1

Mechanical and Surgical Management

- Epithelial Debridement
- Prokera Amnionic 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
Sutureless Amniotic Membranes

- **Sutureless Amniotic membrane**
  - 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, bed side
- Monitor healing by fluorescein and IOP by Tonopen™ without removal
- Does not interfere with antibiotic penetration

**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

**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

**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 65778 (the CPT code) Avg reimbursement $1670.34

**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

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

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

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

Phototherapeutic Keratectomy (PTK)

- Use of excimer laser to smooth Bowman’s
- Epithelium removed manually or with blade / alcohol
- Often used for recalcitrant cases

Objective

- remove enough of the superficial Bowman’s layer to permit formation of a new basement membrane with adhesion structures

Technique

- Debride the epithelium in the involved area
- Use large spot size (5 mm)
- Apply 16 pulses
- No optical effect is seen with such a superficial ablation

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

Alcohol Delamination

- 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

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

PTK 46-100%
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 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

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


More studies needed
**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.

**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.

**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

**Mechanical 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 >>> DCN
- Epi Debridement >>> BSCL 12 weeks >>> DCN
- ASP >>> BSCL 12 weeks >>> DCN
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

47 wm. Don E
- OHx
  - EBMID OS-OD and Hx, Trauma OS with RCE OS
  - 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

35 year old Caucasian female, Sheila F.
- Initial visit ~ 3 years ago
  - Traumatic corneal abrasion OD
  - Treated with BCL, antibiotics, lubrication
  - Healed completely within 3 days

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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 11 months

Patient returns 6 months later with RCE
- Treated with BCL, antibiotics, lubrication
- Resolution within 1 week
- Recurrences ~ 4 months

New treatment recommended:
- BCL x 3 months, replacing every 3 weeks
- Lotemax BID OU x 1 month, FreshKote 2-4x/day
- Doxycycline 20 mg BID x 2 months
- Recurrences ~ 12 months
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 most likely a combination Tx
  - Trial and error to find the best combo for each patient

Thank You.

Please feel free to contact us:
Nicholas Colatrella, OD, FAAO, Dipl ABO, ABCMO
NColatrella@pineconevisioncenter.com
Jeffrey Varanelli, OD, FAAO, Dipl ABO
SECJRVOO@gmail.com

Don’t forget session evaluation