

RECURRENT CORNEAL EROSION:

Strategies To Promote Corneal Healing

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FINANCIAL DISCLOSURES

- EYEVANCE
- NOVARTIS
- TEARLAB

CORNEA

Responsible for 70% of the refractive power of the eye¹

Metabolism²

- Avascular to maintain clarity
- Nutrients are supplied and waste products removed without blood circulation
 - Tear film supplies nutrients anteriorly
 - Aqueous humor supplies nutrients posteriorly

¹ Courville CB, Smolek MK, and Klyce SD. Contribution of the Ocular Surface to Visual Optics. Exp Eye Res. Sept 2003;78:417.
² Bowling B. Cornea. Kanski's Clinical Ophthalmology: A Systematic Approach. Elsevier. 2016:168.

CORNEA

Composed of five layers³

- Epithelium
- Bowman's layer
- Stroma
- Descemet's membrane
- Endothelium

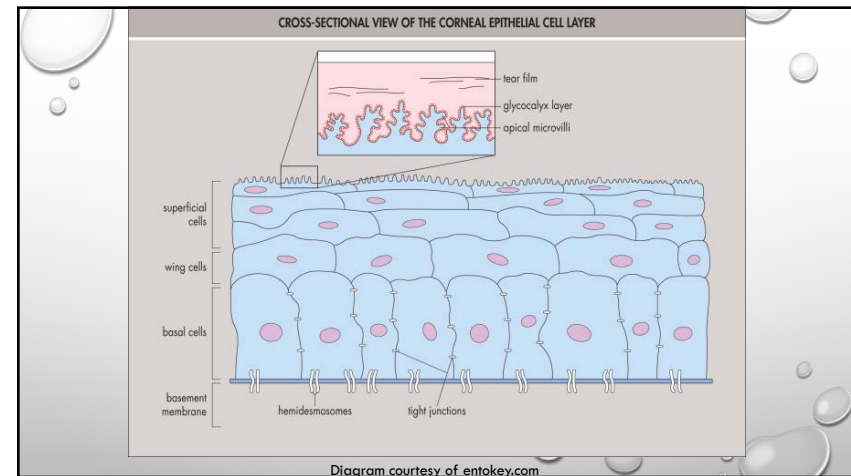
³ Remington LA. Cornea and Sclera. Clinical Anatomy of the Visual System. Elsevier. 2013:10-28.

CORNEAL EPITHELIUM

Squamous surface cells⁴

- Comprised of 2 layers of thin, flat cells
- Squamous cells slough into tear film every few days, replaced by underlying cells
- Squamous cells are joined by tight junctions, forcing fluids through the cells
 - Desmosomes
 - Zonula occludens

⁴Remington LA. Cornea and Sclera. Clinical Anatomy of the Visual System. Elsevier. 2013;10-278.



CORNEAL EPITHELIUM

Wing cell layer

- Comprised of layers of 2-3 thicker cells
- Wing cells have processes (wings) which fill in gaps between underlying cells
- Connected to other cells by desmosomes

CORNEAL EPITHELIUM

Basal cell layer

- Thicker, columnar cells
- Joined to underlying basement membrane via adhesional complexes
- Cellular mitosis
 - Basal cells migrate upwards, replacing squamous cells
 - Basal cells are replaced by cells migrating from the corneal periphery
 - The **ENTIRE** epithelium is replaced in 7 days

CORNEAL EPITHELIUM

Basement membrane⁵

- An acellular layer secreted by overlying basal cells
- Critical in limiting interactions between epithelium and stroma
- Composed of:
 - Collagens
 - Laminins
 - Proteoglycans
 - Nidogens

⁵ Torricelli AAM, Singh V, Santiago MR, Wilson SE. The Corneal Epithelial Basement Membrane: Structure, Function, and Disease. Invest Ophthalmol Vis Sci. 2013. 54(9): 6390-400.

CORNEAL EPITHELIUM

Basement membrane functions

- Anchoring adjacent cells
- Migration, differentiation, and maintenance of epithelial cell differentiation
- Control cellular functions by binding and modulating concentrations of growth factors and cytokines
- Limits the fibrotic (scarring) response in the stroma

⁵ Torricelli AAM, Singh V, Santiago MR, Wilson SE. The Corneal Epithelial Basement Membrane: Structure, Function, and Disease. Invest Ophthalmol Vis Sci. 2013. 54(9): 6390-400.

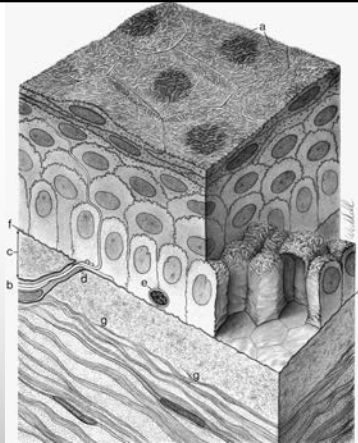


Photo courtesy of Clinical Anatomy of the Visual System, Elsevier, 2013.

BOWMAN'S LAYER

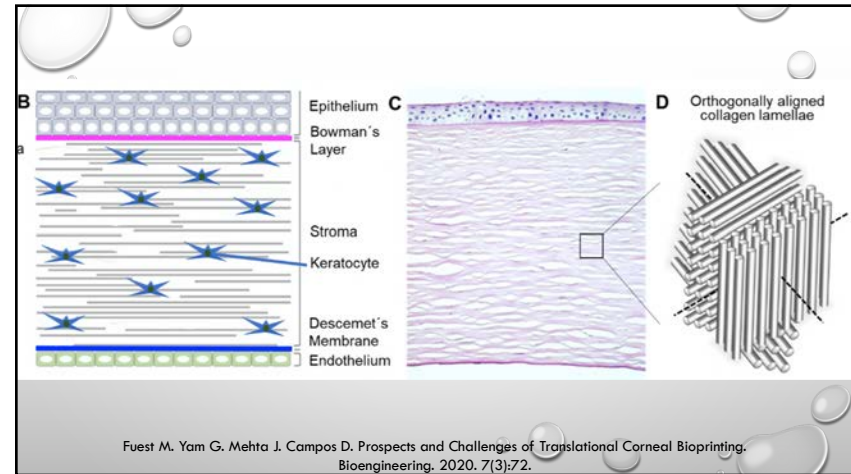
- Not a true membrane⁶
- An acellular transition between basement membrane and stroma

⁶ Sridhar MS. Anatomy of Cornea and Ocular Surface. Indian J Ophthalmol. 2018. 66(2):190-194.

STROMA

- Comprises 90% of corneal thickness⁷
- Composition
 - Keratocytes (corneal fibroblasts)
 - Produce collagen and glycosaminoglycans
 - Build the extracellular matrix
 - Lamellae
 - Collagen fibrils
 - Arranged in systematic bundles that run parallel to the corneal surface
 - Proteoglycans
 - Fill in spaces between keratocytes and lamellae
 - Lumican regulates collagen matrix to maintain corneal clarity

⁷ Remington LA. Cornea and Sclera. Clinical Anatomy of the Visual System. Elsevier. 2013:10-278.



Fuest M, Yam G, Mehta J, Campos D. Prospects and Challenges of Translational Corneal Bioprinting. *Bioengineering*. 2020. 7(3):72.

CELLULAR ADHESIONS BETWEEN EPITHELIUM AND STROMA

Chemical bond – cellular receptors create a chemical bond between cells and extracellular matrix⁸ (ECM)

Adhesion complexes anchor basal cells to stroma

- Hemidesmosomes
- Anchoring filaments
- Anchoring fibrils
- Type VII collagens

Organized disruption of adhesions is necessary to facilitate corneal healing

⁸ Solomon A, Holland EJ, Marnis MJ, Lee WB. Corneal Epithelial Adhesion Disorders. *Ocular Surface Disease: Cornea, Conjunctiva, and Tear Film*. Elsevier. 2013:195-203.

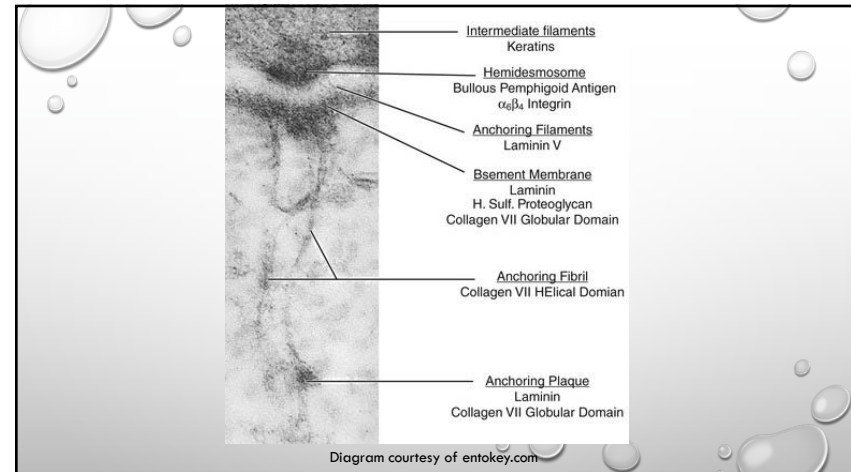


Diagram courtesy of entokey.com

NORMAL CORNEAL WOUND HEALING

Cellular migration⁹

- Temporary change in cellular organization
- Adjacent cells migrate as a sheet, maintaining cell to cell junctions
- Cellular mitosis stops temporarily
- Migrating cells maintain temporary focal adhesions with underlying ECM
- Both basal cells and wing cells participate in formation of the leading edge

⁹ Liu CY, Kao WY. Corneal Epithelial Wound Healing. Prog Mol Biol Transl Sci. 2015. 134:61-71.

NORMAL CORNEAL WOUND HEALING

Cellular proliferation and differentiation

- Remains similar to normal
- No cellular proliferation at leading edge
- Basal cells proliferate at and migrate from the limbus

NORMAL CORNEAL WOUND HEALING

Basement membrane disassembly

- Inflammatory cells release proteases to break down basement membrane (BM)
- Epithelial cells release metalloproteinases (MMPs) to help degrade BM
- Temporary BM disassembly aids cellular migration
- Wound healing is not complete until the BM is fully restored
- BM critical in limiting bidirectional interactions between epithelium and stroma
 - Inhibits stromal fibrosis and haze
 - Promotes corneal clarity

RECURRENT CORNEAL EROSION (RCE)

• Causes of RCE:

- INJURY - May be a result of aberrant corneal wound healing
- DISEASE - May be due to defects in the basement membrane
 - Anterior basement membrane dystrophy (ABMD)
 - Diabetes

RECURRENT CORNEAL EROSION

Acute phase¹⁰

- BM absent in areas, no adhesional complexes are present
- Lack of BM results in episodic loss of epithelium

¹⁰Diez-Felgado E, Durán JA. Optical Coherence Tomography Findings in Recurrent Corneal Erosion Syndrome. *Cornea*. 2015. 34(3):290-5.

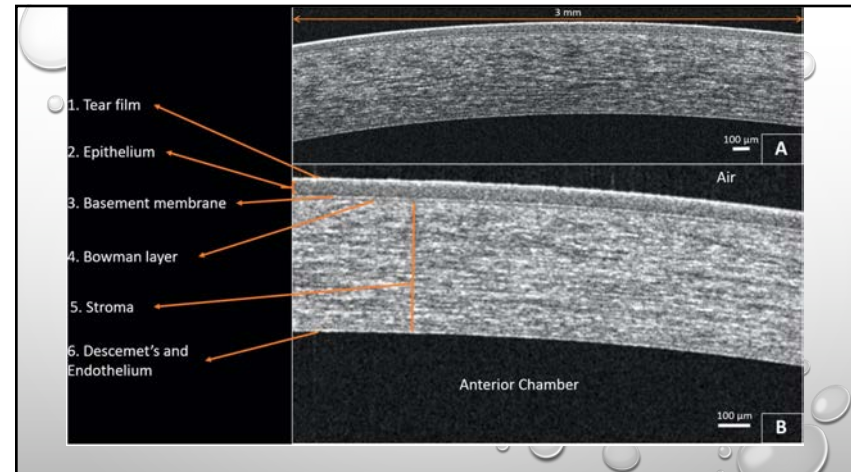
RECURRENT CORNEAL EROSION

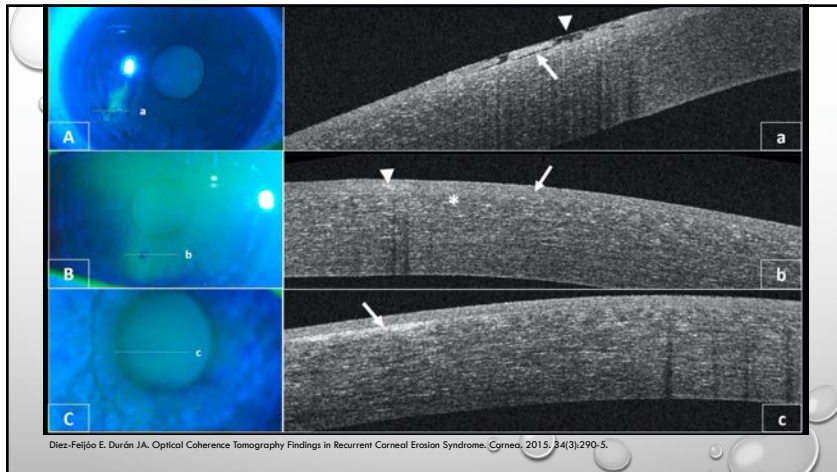
Chronic phase

- Aberrant BM entraps epithelium beneath it, leads to BM disruption when cells migrate
- Abnormal junctional complexes form
 - Cellular debris becomes trapped beneath epithelium
 - Causes areas of thickened epithelium
- These abnormalities cause further BM disruption (vicious cycle)

RECURRENT CORNEAL EROSION

- Diabetics may present with BM defects and RCE
 - Defects can occur without injury
 - Diabetics may lack the necessary building blocks to restore an intact BM
 - Nidogens
 - Laminins
 - Integrins





RCE CLINICAL PRESENTATION

Patient complaints

- Sudden onset eye pain, often on awakening
- Tearing
- Redness
- Blurred vision
- Photophobia

Thorough case history important to determine etiology

RCE CLINICAL PRESENTATION

Slit lamp findings

- Conjunctival injection
- Corneal epithelial defects
- Epithelial edema and microcysts
- Thickened epithelium/ABMD

Incidence 1:150 patients with a history of corneal injury¹¹

Most patients age 30 to 60¹²

¹¹ Solomon A, Holland EJ, Mannis MJ, Lee WB. Corneal Epithelial Adhesion Disorders. Ocular Surface Disease: Cornea, Conjunctiva, and Tear Film. Elsevier. 2013:195-203.

¹² Diez-Felgado E, Durán JA. Optical Coherence Tomography Findings in Recurrent Corneal Erosion Syndrome. Cornea. 2015; 34(3):290-5.

RCE DIFFERENTIAL DIAGNOSIS

- Herpes simplex virus keratitis
- Exposure keratopathy
- Neurotrophic keratitis
- Conjunctival foreign body
- Dry eye disease
- Infectious keratitis

CAUSES OF RCE

- Corneal injury (45-67% of cases)
- Anterior Basement Membrane Dystrophy (ABMD)
- Diabetes
- Dry eye disease/Meibomian gland dysfunction
- PRK/LASIK
- Undetermined (18.8%)¹³

¹³ Diaz-Feijóo E, Grau AE, Abusleme EI, Durán JA. Clinical Presentation and Causes of Recurrent Corneal Erosion Syndrome: Review of 100 Patients. *Cornea*. 2014; 33(6): 571-5.

DIABETES AND RCE

- Diabetes is a strong risk factor for RCE¹⁴
- Diabetes is a predictor of longer recovery, prolongs healing by avg. of 7 weeks
- Diabetic corneas are slow to establish normal epithelial to stromal adhesions¹⁵
 - Decreased expression of binding agents
 - Laminins serve vital function in BM structural organization
 - Nidogens are "link proteins" that bind laminins to collagen
 - Reduced formation of hemidesmosomes
 - Decreased integrin synthesis
 - Abnormal expression of growth factor

¹⁴ Torricelli AAM, Singh V, Santhiago MR, Wilson SE. The Corneal Epithelial Basement Membrane: Structure, Function, and Disease. *Invest Ophthalmol Vis Sci*. 2013; 54(9): 6390-400.

¹⁵ Namba H, Mimura T, Mizuno Y, et al. Clinical Course and Risk Factors of Recurrent Corneal Erosion. *Medicine*. 2019; 98(16): 1-B.

RCE TREATMENT

GOALS:¹⁶

- Allow epithelium to heal in acute presentations
 - Restore epithelial barrier to infection
 - Improve patient comfort
- Prophylaxis - no clear consensus on treatment to prevent recurrences

¹⁶ Thakrar R, Hemmati HD. Treatment of Recurrent Corneal Erosions. *American Academy of Ophthalmology* [homepage on the Internet]. March 1, 2013. Available from: <https://www.aao.org/eye/clinical/treatment-of-recurrent-corneal-erosions>. Accessed March 24, 2020.

RCE TREATMENT

- AAO recommends individualized approach to therapy¹⁷
 - No set guidelines for treatment
 - Topical therapies
 - Medical therapies
 - Surgical intervention
- 59% of RCE cases continued to have symptoms after 4 years of treatment¹⁸ (1998)

¹⁷ Thakrar R, Hemmati HD. Treatment of Recurrent Corneal Erosions. *American Academy of Ophthalmology* [homepage on the Internet]. March 1, 2013. Available from: <https://www.aao.org/eye/clinical/treatment-of-recurrent-corneal-erosions>. Accessed March 24, 2020.

¹⁸ Solomon A, Holland EJ, Mannis MJ, Lee WB. Corneal Epithelial Adhesion Disorders. *Ocular Surface Disease: Cornea, Conjunctiva, and Tear Film*. Elsevier. 2013:195-203.

RCE TREATMENT- INITIAL THERAPY

Preservative free artificial tears at least QID and lubricant UNG QHS

Topical antibiotic treatment if the epithelium is compromised

Topical cycloplegic and/or oral analgesic for pain relief

Hypertonic saline drops or UNG once the epithelium is intact (???)

- Consider Freshkote as an alternative

RCE TREATMENT- INITIAL THERAPY

- Why preservative free artificial tears?
- Benzalkonium chloride (BAK) causes damage to human ocular cells
 - Symptoms: burning, FBS, dry eye, tearing, itchy eyelids
 - Signs: SPK, conjunctival injection, staining, reduced tear production and TBUT, increased osmolarity
 - Histopathology: reduced goblet cells, increased inflammatory cells and markers
 - Effects are dose dependent
 - "Switch" studies show improvement in signs and symptoms, reduced OSDI in 97% DED patients
- Alternative preservatives are a good option
 - Polyquaternium-1 (POLYQUAD)
 - "Disappearing" preservatives: sodium perborate, Stabilized Oxychloro Complex (SOC), Sofzia

Walsh K, Jones L. The use of preservatives in dry eye drops. Clin Ophthalmol. 2019(13): 1409-25.

RCE TREATMENT- INITIAL THERAPY

Freshkote

- Blend of polyvinyl alcohol results in high oncotic pressure (colloidal osmolarity)
 - Causes water to leave epithelial cells
 - Facilitates epithelial adhesion
- Preservative free
 - 10mL multidose bottle
 - Microbiologically sterile up to 90 days
- Often stings, reassure patients

RCE TREATMENT- MEDICAL THERAPIES

BANDAGE CONTACT LENS (BCL)

- Can be worn up to 3 months
- BCL prevents microerosions, allows full restoration of adhesional complexes¹⁹
- Effectiveness²⁰
 - Symptoms resolve faster with BCL than lubricants alone (5 weeks vs. 9 weeks)
 - 71% showed complete resolution, no difference between lubricants only or with BCL

¹⁹ Lin SR, Aldave AJ, Chodosh J. Recurrent Corneal Erosion Syndrome. Br J Ophthalmol. 2019. 103:1204-8.

²⁰ Ahad MA, Anandan M, Tah V, et al. Randomized Controlled Study of Ocular Lubrication Versus Bandage Contact Lens in the Primary Treatment of Recurrent Corneal Erosion Syndrome. Cornea. 2013. 32(10): 1311-14.

RCE TREATMENT- MEDICAL THERAPIES

TREAT COMORBIDITIES

- If aqueous deficient dry eye disease, consider punctal plugs²¹
- Treat MGD and blepharitis, which can exacerbate RCE

²¹ Thakrar R, Hemmati HD. Treatment of Recurrent Corneal Erosions. American Academy of Ophthalmology [homepage on the Internet]. March 1, 2013. Available from: <https://www.aao.org/eye-health/treatment/recurrent-corneal-erosions>. Accessed March 24, 2020.

²² Solomon A, Holland EJ, Mannis MJ, Lee WB. Corneal Epithelial Adhesion Disorders. Ocular Surface Disease: Cornea, Conjunctiva, and Tear Film. Elsevier. 2013:195-203.

RCE TREATMENT- MEDICAL THERAPIES

Combination oral tetracyclines and topical steroids

Doxycycline suppresses matrix metalloproteinases (MMP's)²³

- MMP's are necessary for BM disassembly during wound healing
- MMP's are upregulated in RCE
- MMP's can prevent BM restoration when upregulated
- Doxycycline reduces MMP-9 activity in corneal epithelial cells by 70%

Doxycycline and topical steroids both reduce the activity of pro-inflammatory cytokines

²³ Ramamurthi S, Rahman MQ, Dutton GN, Ramoesh K. Pathogenesis, Clinical Features, and Management of Recurrent Corneal Erosions. Eye. 2006. 20:638-40.

COMBINATION ORAL DOXYCYCLINE AND TOPICAL STEROIDS

Dosage

- 50 mg doxycycline QD to BID for 4 to 6 weeks
- Topical steroids starting at TID to QID, then taper, for 4 weeks total

Efficacy²⁴

- 71% free of symptoms at 8 weeks
- All but one patient reported improvement

²⁴ Wang L, Tsang H, Coronea M. Treatment of Recurrent Corneal Erosion Syndrome Using the Combination of Oral Doxycycline and Topical Corticosteroid. Clin Exp Ophthalmol. 2008. 36(1):8-12.

COMBINATION ORAL DOXYCYCLINE AND TOPICAL STEROIDS

Potential adverse effects²⁵

- GI upset
- Photosensitivity
- Potential for esophageal ulceration
- Contraindicated with blood thinners

²⁵ Wang L, Tsang H, Coronea M. Treatment of Recurrent Corneal Erosion Syndrome Using the Combination of Oral Doxycycline and Topical Corticosteroid. Clin Exp Ophthalmol. 2008. 36(1):8-12.

RCE TREATMENT- MEDICAL THERAPIES

Autologous serum tears²⁶

- Patients blood serum combined with sterile saline
- Provide growth factors and cytokines to the ocular surface
- 80% of patients remained free of symptoms after 12 months
- Availability
 - Local specialty pharmacy
 - Vital Tears

²⁶ Miller DD, Hassan SA, Simmons NL, Stewart MW. "Recurrent Corneal Erosion: A Comprehensive Review. Clin Ophthalmol. 2019. 13:328.

RCE TREATMENT- MEDICAL THERAPIES

Self-retained amniotic membrane²⁷

- Donated amniotic tissue applied in office to promote corneal healing
 - Prokera (Biotissue) – cryopreserved
 - Must be kept in a freezer
 - Retains more biological components
 - Can be more challenging to insert and remove
 - Atlas, Triad, Ambiodisk etc. – dehydrated
 - Easier storage, longer shelf life
 - Loss of biologics
 - Easier to tolerate
 - Costs less

²⁷ Thomas J, Tighe, S, Sheha H, et al. Corneal Nerve Regeneration after Self-Retained Cryopreserved Amniotic Membrane in Dry Eye Disease. J Ophthalmol. 2017; 64:4918.

PROKERA SELF-RETAINED AMNIOTIC MEMBRANE

PROKERA²⁸

- Retains key active components of the Extra Cellular Matrix
- Key biologic: Heavy Chain Hyaluronic Acid/Pentraxin-3 complex (HC-HA/PTX3)
- Dried amnions contained NO:
 - Molecular weight HA
 - Lubricin
- PTX3 is abundant in cryopreserved
- Only product FDA cleared to:
 - Reduce inflammation
 - Promote epithelial and corneal nerve regeneration
 - Prevent scarring

²⁸ MacDonald, M, Sheha H, Tighe S, et al. Treatment Outcomes in the Dry Eye Amniotic Membrane (DREAM) Study. Clin Ophthalmol. 2018;12:677-81.

PROKERA

CLINICAL RECOMMENDATIONS:

- Placed for 3-5 days
- Recommend a tape tarsorrhaphy, at least at bedtime
- Advise use of preservative free artificial tears
- Best to insert on Monday or Tuesday, remove on Friday
- Healing continues for weeks after removal

RCE TREATMENT- SURGICAL INTERVENTIONS

Anterior stromal puncture²⁹

- A needle is passed through the stroma at 0.5mm intervals
- Promotes firm epithelial adhesions
- Produces scars, use is limited to peripheral cornea
- 80% success rate in preventing recurrences
- Similar procedure can be done with a Nd:YAG laser

²⁹ Miller DD, Hasan SA, Simmons NL, Stewart MW. "Recurrent Corneal Erosion: A Comprehensive Review. Clin Ophthalmol. 2019. 13:328.

RCE TREATMENT- SURGICAL INTERVENTIONS

Epithelial debridement by alcohol delamination³⁰

Procedure

- 20% alcohol is applied to the cornea
- Excess alcohol removed with sponge
- Irrigate the eye
- Epithelium becomes loose, can be removed with a spatula
- Follow up care
 - Bandage CL
 - Topical antibiotics

³⁰ Miller DD, Hasan SA, Simmons NL, Stewart MW. "Recurrent Corneal Erosion: A Comprehensive Review. Clin Ophthalmol. 2019. 13:328.

RCE TREATMENT- SURGICAL INTERVENTIONS

Epithelial debridement by alcohol delamination

Treatment results

- Removes epithelium and basement membrane
- Leaves Bowman's layer intact
 - No risk of corneal scarring
 - Allows normal healing due to smooth Bowman's layer

Approximately 75 to 80% success rate

RCE TREATMENT- SURGICAL INTERVENTIONS

Epithelial debridement with diamond burr polishing³¹

Procedure

- Epithelial debridement using a cellulose sponge or a spatula
- Treat the central 7 to 10 mm of the cornea
- Follow it with diamond burr polishing to remove Bowman's layer
- Removes aberrant areas of basement membrane
- Debridement more effective with DBP than without

Follow up care

- Bandage CL
- Topical antibiotics

³¹ Miller DD, Hasan SA, Simmons NL, Stewart MW. "Recurrent Corneal Erosion: A Comprehensive Review. Clin Ophthalmol. 2019. 13:328.

RCE TREATMENT- SURGICAL INTERVENTIONS

Epithelial debridement with diamond burr polishing³²

Efficacy

- 97% resolution, average of 32 months follow up
- Lin et al (2015) study of 91 eyes

Potential side effects

- Subepithelial haze
- 14% in Lin et al study

³¹ Miller DD, Hasan SA, Simmons NL, Stewart MW. "Recurrent Corneal Erosion: A Comprehensive Review. Clin Ophthalmol. 2019. 13:328.

RCE TREATMENT- SURGICAL INTERVENTIONS

• Phototherapeutic keratectomy³³

- Uses a laser to remove the epithelium
- Good short term success rate (60 to 100%)
- Few long-term studies
- Potential side effects
 - Hyperopic shift
 - Iatrogenic astigmatism
 - Corneal haze

³³ Miller DD, Hasan SA, Simmons NL, Stewart MW. "Recurrent Corneal Erosion: A Comprehensive Review. Clin Ophthalmol. 2019. 13:328.

PATIENT CASE – 59 YO WM

Initial visit

- Complaint of OD blurry, scratchy, watering
- No history of ocular injury
- History of Type II DM
- VA OD 20/200 and OS 20/20-, OD improved to 20/50 with refraction
- Exam
 - OD 1+ conjunctival injection
 - OD focal epithelial defects slightly inferior to central cornea with surrounding epithelial edema
 - Irregular areas of BM noted OD only

PATIENT CASE – 59 YO WM

• Initial Treatment

- TobraDex QID x 1 week, then BID x 1 week
- Blink gel drops QHS

PATIENT CASE – 59 YO WM

Follow-up #1 – 2 days later

- VA OD 20/80- and OS 20/20, OD improved to 20/30 with PH
- Exam
 - Reduced corneal edema
 - Small, persistent epithelial defect
- Treatment
 - Continue TobraDex QID, then BID
 - Change to 5% sodium chloride UNG QHS
 - Follow up in 1 week

PATIENT CASE – 59 YO WM

• Follow-up #2 – 1 week later

- Patient reported vision had been clear until he woke up that morning, worsening since then
- VA OD 20/60- and OS 20/20
- OD improved to 20/30 with refraction
- Exam
 - Persistent corneal edema
 - Small, persistent epithelial defect
- Treatment
 - Discussed possibility of referral for DBP or PTK, decided on medical tx
 - Continue TobraDex BID until gone
 - Continue 5% sodium chloride UNG QHS
 - Add po doxycycline 100 mg QD x 60 days and FreshKate QID

PATIENT CASE – 59 YO WM

• Follow-up #3 – 1 week later

- VA OD 20/30, refracted to 20/20
- Exam
 - NO corneal edema
 - NO epithelial defect
- Patient free of recurrences at exam 1 month later and 1 year later

APPLYING THESE PRINCIPLES TO OTHER CONDITIONS

- Dry Eye Disease
 - Persistent Epithelial Defects
 - Filamentary Keratitis
- Band Keratopathy
- Nodular Corneal Degeneration
- Chemical Burns
- Corneal ulcers
- Neurotrophic Keratitis

THANK YOU!

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