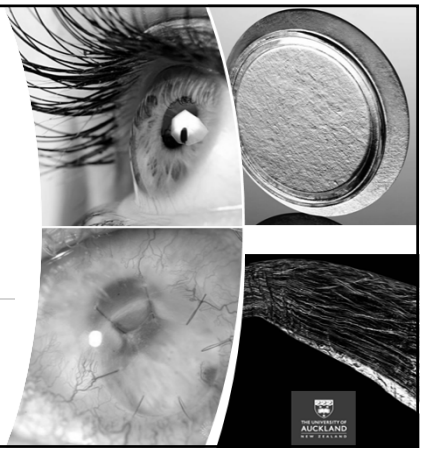
[redacted]

Persistent Epithelial Defects



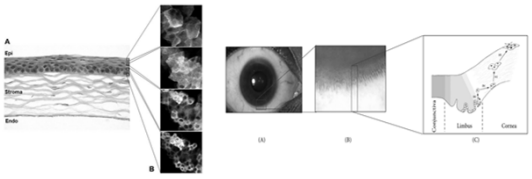
Mo Ziaei
MBChB (Hons) MD FRCOphth FRANZCO

Cornea & anterior segment specialist
Senior lecturer

Cornea epithelium

- The epithelium is made up of nonkeratinized stratified squamous epithelium.
- The corneal epithelium is composed fairly uniformly of 5–7 layers of cells.
- Cornea epithelial cells have a lifespan of 7 to 10 days undergoing involution, apoptosis, and desquamation.
- The epithelium is maintained by a specialized stem cell population, known as limbal stem cells (LSCs), located in the basal region of the limbus.
- The XYZ hypothesis proposes that the maintenance of the corneal epithelium can be represented by the formula:

X (proliferation) +Y (centripetal migration) =Z (desquamation)



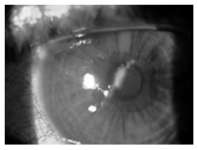
•Ziaei M, Greene C, Green CR. Wound healing in the eye: Therapeutic prospects. Adv Drug Deliv Rev. 2018;126:162-76.

Cornea epithelium

- In normal conditions after an injury to the cornea, the epithelial layer undergoes an active repair process over 7-10 days.
- Highly regulated process involving growth factors, cellular signalling, proliferation, migration and extracellular matrix remodelling.

[redacted]

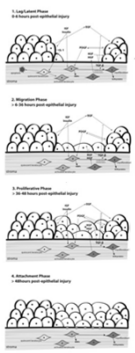
3 days later



Cornea epithelium wound healing

- Corneal wound healing is a cytokine mediated interactions between epithelial cells, stromal keratocytes, corneal nerves, and cells of the immune system control this process.

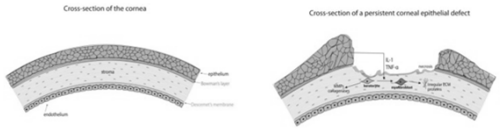
1. **Latent phase:** no cell movement or change in cell numbers is evident but there is an increase in metabolic activity and a reorganization of cell structures is observed. This is accompanied by an increased synthesis of several cytoskeletal proteins.
2. **Migration phase:** cells surrounding the wound migrate over and cover the denuded area.
3. **Proliferation phase** in which epithelial cells proceed to divide and differentiate, restoring the epithelium's original structure. The proliferative response appears to be compartmentalized to the limbus.
4. **Attachment phase:** is characterized by the establishment of cell-substrate attachments observed in non-motile epithelium.



•Ziaei M, Greene C, Green CR. Wound healing in the eye: Therapeutic prospects. Adv Drug Deliv Rev. 2018;126:162-76.

Persistent epithelial defects

- Normal epithelial defects typically recover within 7-10 days.
- PED will not heal even after 2 weeks and is usually refractory to standard therapies and supportive care.
- PEDs occur when there is a failure of mechanisms which promote corneal epithelialization.
- PEDs commonly extend into the stromal layer, causing stromal melting, secondary ulceration, and stromal scarring.

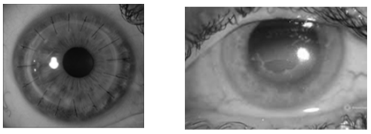


•Katzman LR, Jeng BH. Management strategies for persistent epithelial defects of the cornea. Saudi J Ophthalmol. 2014;28(3):168–72.
•Dahlgren MA, Dhaliwal A, Huang AW. Persistent Epithelial Defects. 2008:749–59.

Epidemiology

- The incidence of PED is unknown.
- Estimates are that the annual incidence of PED is less than 200,000 cases in the USA (0.06%).
- The incidence of PED following a corneal transplant is much higher at around 7,500 cases per year (16%).
- Risk factors after keratoplasty:

1. Male sex
2. Age >60 years
3. Comorbid systemic disease such as diabetes, rheumatic diseases and cancer therapy.

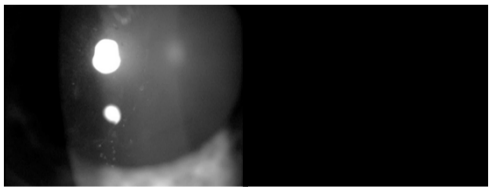


•Wirostko B, Rafii M, Sullivan DA, Morelli J, Ding J. Novel Therapy to Treat Corneal Epithelial Defects: A Hypothesis with Growth Hormone. Ocul Surf. 2015;13(3):204–12.e1.

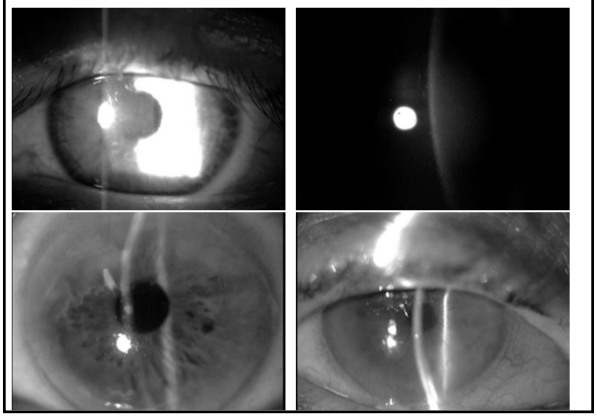
Etiology

Defective adhesion

Defective epithelial adhesion	Recurrent corneal erosions EBMD Toxic keratopathy Salzmann's nodules Band keratopathy Bullous keratopathy Vitamin A deficiency Scarring and trauma	- Defective epithelial adhesion - Deficient or abnormal basement membrane - Overproduction of MMPs -Disruption of epithelial cell migration

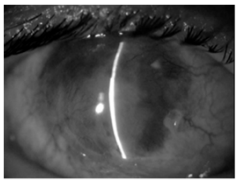


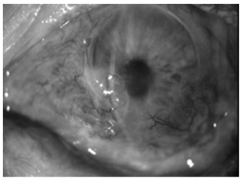
Defective adhesion



Limbal stem cell deficiency

Limbal stem cell deficiency	Stevens Johnson syndrome Chemical injury Trauma	Deficiency of limbal stem cells

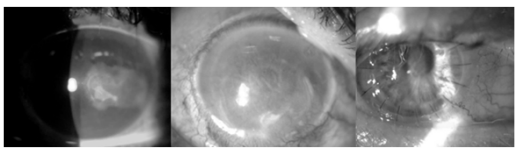




•Ziaei M, Greene C, Green CR. Wound healing in the eye: Therapeutic prospects. Adv Drug Deliv Rev. 2018;126:162-76.

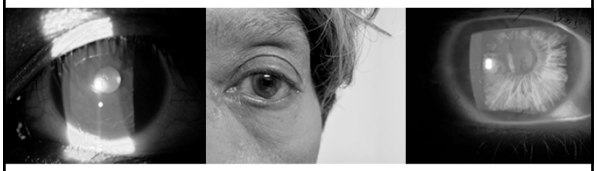
Inflammation

Inflammation	Following infectious keratitis Autoimmune diseases Sjögren's syndrome Mucous membrane pemphigoid Graft vs. host disease Peripheral ulcerative keratitis	- Over-activity of cytokines (TNF- α and IL-1) - Reduced production of growth factors by keratocytes impairing proliferation and migration of epithelial cells.



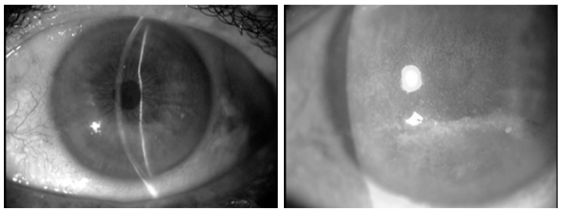
Mechanical

Mechanical	Lagophthalmos Entropion or ectropion Trichiasis Blepharospasm Pseudomembranes Tarsal FB/scars Trachoma	-Recurrent abrasions can result in depletion of epithelial stem cells - Corneal erosions can occur from eyelid abnormalities

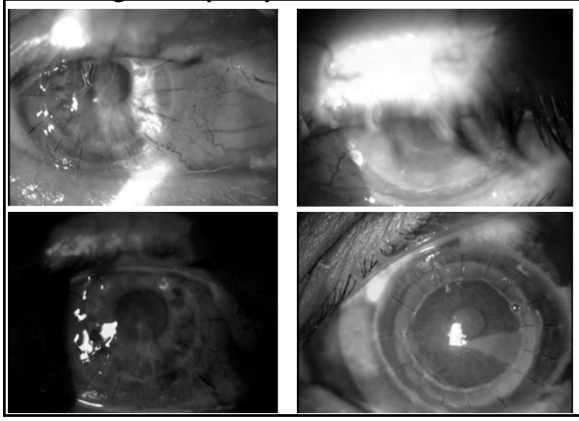


Neurotrophic cornea

Neurotrophic	Diabetes mellitus Severe dry eye syndrome Current or past herpetic keratitis Anesthetic abuse Traumatic or postoperative nerve damage	Local or systemic damage to trigeminal nerve



Following keratoplasty



Diagnosis

Diagnosis

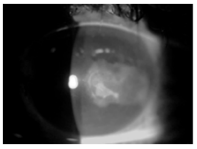
- A comprehensive patient history should be taken to highlight any possibilities of a previous herpetic infection, diabetes, immune disorders, prior surgery (LVC) or injury.

- **Slit lamp exam**

1. Fluorescein instillation to monitor the size, location, and depth of the defect.
2. Thinning of the cornea
3. Vascularisation
4. Infiltration
5. Corneal sensation
6. Tear film status

- **Eyelid exam**

Check for lid position, laxity and lagophthalmos.



•Katzman LR, Jeng BH. Management strategies for persistent epithelial defects of the cornea. Saudi J Ophthalmol. 2014;28(3):168–72.
•Dahlgren MA, Dhaliwal A, Huang AJW. Persistent Epithelial Defects. 2008:749–59.

Treatment

Treatment

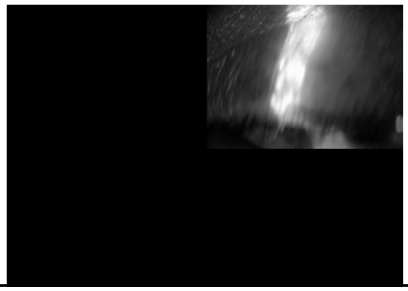
PEDs should be treated within 7-10 days to avoid secondary complications.

1. Treat underlying cause
2. Eliminate iatrogenic causes (i.e. benzalkonium chloride)
3. Aggressive lubrication with preservative-free drops and ointments
4. Bandage soft contact lenses (BCL)
5. Punctal plugs
6. Tape lids at night if lagophthalmos is present

•Ziaei M, Greene C, Green CR. Wound healing in the eye: Therapeutic prospects. Adv Drug Deliv Rev. 2018;126:162-76.

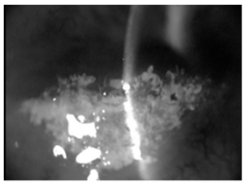
Adjuvant treatments

1. Oral Tetracyclines
2. Epithelial debridement
3. Autologous serum
4. Toxin or suture tarsorrhaphy
5. Cyanoacrylates glue
6. Amniotic membrane transplantation



Antibiotics & steroid controversy

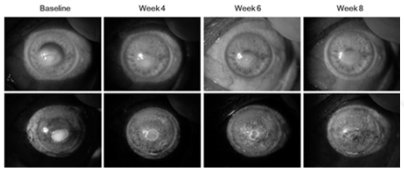
- Prophylactic topical antibiotics (QID) probably reduce the risk of infectious keratitis particularly if a BCL has been placed.
- A PF 3rd or 4th generation fluoroquinolone is ideal but difficult to access in NZ.
- Corticosteroids, if applied in conjunction with appropriate antibacterial therapy, may reduce the inflammatory component of the disease and minimise scarring.
- Topical corticosteroids are controversial in treating PED because they may cause tissue destruction, stromal melting, and an increased risk of microbial keratitis.



•Barba KR, Samy A, Lai C, et al. Effect of topical anti-inflammatory drugs on corneal and limbal wound healing. J Cat Ref Surg. 2000;26:893–7.
•Tomas-Barveran S, Fagerholm P. Influence of topial treatment on epithelial wound healing and pain in the early postoperative period following photorefractive keratectomy. Acta Ophthalmol Scand. 1999;77:135–8.

Novel treatments

1. Nexagon
2. Topical growth factors EGF, IGF-1, HGF
3. Recombinant human nerve growth factor (rhNGF)
4. Matrix regenerating agent, ReGeneraTing Agent (RGTA)
5. Amniotic membrane extract eye drops (AMEED)



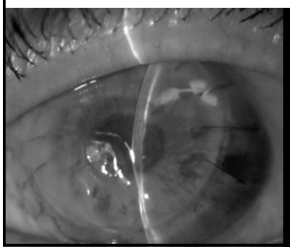
•Ziaei M, Greene C, Green CR. Wound healing in the eye: Therapeutic prospects. Adv Drug Deliv Rev. 2018;126:162-76.
•Bonini S, Lambiase A, Rama P, et al, for the Reparo Study Group. Phase II randomized, double-masked, vehicle-controlled trial of recombinant human nerve growth factor for neurotrophic keratitis. Ophthalmology. 2018;125:1332-43.

Complications

Corneal melt and perforation

- The consequences of an untreated PED include:

1. Infection
2. Anterior stromal scarring
3. Melting
4. Neovascularization
5. Ulceration
6. Perforation



Conclusions

- An epithelial defect lasting longer than 14 days is referred to as a PED.
- The etiology of PED is diverse.
- Treatment involves dealing with the underlying risk factors and a stepladder approach to encourage epithelial healing.
- PEDs refractory to treatment are uncommon but can have devastating consequences.
- Early recognition and referral to a corneal specialist can improve prognosis in thus patient group.