External Diseases for the Pediatric Ophthalmologist

Inez BY Wong Ms/ FRCSEd (Ophth), Ken K Nischal Mr/ FRCOphth

National University Hospital Singapore, Great Ormond Street Hospital for Children United Kingdom

Course outline

There are some common external disease problems that affect children commonly. Among these are allergic conjunctivitis, blepharokeratoconjunctivitis, persistent punctate epithelial erosions and persistent epithelial defect.

Allergic conjunctivitis can range from simple allergic reaction to severe vernal keratoconjunctivitis with secondary glaucoma due to steroid therapy. Strategies will be discussed as to how to manage these conditions with emphasis on newer drugs and therapies available.

Blepharokeratoconjunctivitis can be extremely difficult to treat and may present with recurrent chalazia or marked photophobia with reduced vision. Treatment of the lid margin disease using topical and systemic treatments will be outlined as will management therapies for the functional drying of the eye that may follow.

Persistent epithelial erosions can result in marked rubbing of the eyes. Common etiologies and treatment modalities will be discussed. Types of lubrication and how they may best be utilised will also be outlined.

Persistent epithelial defects may occur due to a variety of reasons but in order to treat these efficiently one must look at the micro-environment of the ocular surface to improve them. Therapeutic modalities may include botulinum induced ptosis, lateral tarsorrhaphy, and if the cornea is thinning, amniotic membrane graft. Rare causes of corneal anesthesia will be discussed.
I. Allergic eye diseases

Ocular allergy is a common problem affecting 20% of the population worldwide, including both adults and children. It encompasses a spectrum of disorders which range from relatively mild acute allergic reactions to more severe and potentially blinding forms such as vernal keratoconjunctivitis. Six main clinical forms have been described.

1. Acute allergic conjunctivitis (AAC)
2. Seasonal allergic conjunctivitis (SAC)
3. Perennial allergic conjunctivitis (PAC)
4. Vernal keratoconjunctivitis (VKC)
5. Atopic keratoconjunctivitis (AKC)
6. Giant Papillary Conjunctivitis (GPC)

The treatment has in the past focused on symptomatic relief, but with better understanding of the immunopathological mechanisms involved, newer therapeutic strategies interventions are being developed.

Immunopathology

The allergic response results from exposure of the conjunctiva to an allergen. SAC and PAC are the only diseases to involve solely Type 1 hypersensitivity, in which the allergen binds to the sensitized IgE antibody on the mast cell, causing the mast cell to degranulate and releasing mediators such as histamine, prostaglandins, and leukotrienes. This early phase response is immediate but a late phase response involving eosinophils and T cells occurs 4-6 hours later.

The other forms of ocular allergies involve a more complex immunological basis and a chronic inflammatory component. In addition to a type 1 hypersensitivity reaction, a delayed type IV hypersensitivity reaction induced by T lymphocytes and macrophages also play a pivotal role. VKC is thought to be a TH2 driven disease, and both T cells and eosinophils are markedly increased in the conjunctiva. Products of degranulation from eosinophils, such as eosinophil cationic protein (ECP), eosinophil granule major basic protein (MBP) are thought to contribute to the more serious corneal symptoms of VKC. AKC and GPC have similar mechanisms but a different chemokine profile.
### Clinical features

<table>
<thead>
<tr>
<th>Disease</th>
<th>Age group</th>
<th>Clinical features</th>
</tr>
</thead>
</table>
| AAC     | Any (especially in children) | • Occurs when a large amount of allergen is accidentally inoculated into the eye  
• Swelling of conjunctiva and lids  
• Intense itching |
| SAC     | 10 - 40 years | • Caused by seasonal allergens such as pollen  
• Itchy, burny, watery eyes  
• Conjunctival redness and oedema +/- papillary reaction |
| PAC     | Similar to SAC | • Caused by allergens present year-round e.g. house dust mite  
• Similar to SAC but symptoms present for at least 1 year |
| VKC     | Onset <10 years | • Boys > girls  
• More prevalent in warm dry climates e.g. Mediterranean, India  
• Majority has family history or personal history of atopy  
• Self-limiting, lasting 2 to 10 years  
• May be unilateral or asymmetrical  
• Conjunctival injection with thick ropy discharge  
• Giant papillae on superior palpebral conjunctiva - “cobblestone” appearance  
• Limbitis  
• Horner-Trantas dots may be present at limbus  
• Punctate epithelial erosions  
• Macrorerosions  
• Shield ulcers |
| AKC     | Young adults 20 – 60 years | • Males > females  
• Associated with atopic dermatitis  
• Chronic and more severe  
• Usually bilateral  
• Scaly and crusty eyelids  
• Papillae upper and lower palpebrae conjunctiva  
• Conjunctival scarring including symblepharon  
• Puntate epithelial erosions  
• Corneal scarring and vascularisation  
• Anterior subcapsular cataracts (5%) |
| GPC     | Any age (contact lens wear) | • Giant papillae on superior conjunctival tarsus  
• Cornea usually spared |
Management

1. Allergen avoidance and lubrication

2. Topical Antihistamines

   Relieve itching and redness, but short acting. Useful for SAC and PAC.
   Second generation selective H1 antagonists
     • levocabastine HCL suspension 0.05% (Livostin) qds
     • emedastine difumarate solution 0.05% (Emadine) qds

   Topical antihistamines (usually 1st generation) combined with vasoconstrictors are usually available without a prescription, e.g. Opcon-A (B&L) which is a combination of naphazoline and pheniramine. Longterm use is not advised as rebound vasodilatation and inflammation may exacerbate the condition.

3. Systemic Antihistamines

   Oral antihistamines are extensively used to control allergic rhinoconjunctivitis. They may also be helpful in patients with severe AKC and VKC. The newer antihistamines are not associated with drowsiness.
     • Loratidine (Claritin) 10mg od (6 years or above)
     • Fexofenadine (Allergra) 60mg bd (30mg bd 6-11 years)

4. Mast Cell Stabilizers

   The mechanism of action is unclear, but there is decrease in degranulation of mast cells in response to an antigen. Therefore they do not relieve existing symptoms and need to be used on a prophylactic basis, or combination with other drugs.
     • Sodium cromoglycate 4% (Cromolyn Sodium) qds
     • Lodoxamide tromethamine 0.1% (Alomide) qds
     • Pemirolast potassium ophthalmic solution 0.1% (Alamast) qds

5. Dual-acting Agents

   Mast cell stabilizer with antihistamine effect (H1 antagonist)
   Also demonstrated to inhibit eosinophil chemotaxis/ activation.
   Rapid relief, with longterm effect.
     • Olopatadine HCL solution 0.1% (Patanol) bd, or 0.2% (Pataday) od
     • Nedocromil sodium 2% (Alocril) bd
     • Ketotifen fumarate solution 0.025% (Zaditor) tds
     • Azelastine HCL solution 0.05% (Optivar) bd

6. NSAIDS

   Topical NSAIDS inhibits the cyclooxygenase enzyme that is essential in the synthesis of prostaglandins. They have been shown to relieve ocular itching in allergic conjunctivitis.
     • ketorolac tromethamine 0.5% (Acular) qds
7. **Steroids**

Topical corticosteroids are extremely effective in controlling inflammation and symptoms, but may be associated with localized ocular complications, including increased intraocular pressure, cataract formation and viral or fungal infections. Short pulses are therefore recommended for acute flare-ups:

- prednisolone acetate ophthalmic suspension 1% (Pred forte), or 0.12% (Pred mild)
- dexamethasone suspension 0.1% (Maxidex)
- fluorometholone ophthalmic suspension 0.1% (FML)

Studies show that weaker steroids such as FML has a lower propensity to increase intraocular pressure than dexamethasone.

Two modified steroids which are derivatives of prednisolone are rapidly inactivated once they enter the anterior chamber thus reducing the risk of raised intraocular pressure.

- Loteprednol etabonate ophthalmic suspension 0.2% (Alrex) or 0.5% (Lotemax)
- Rimexolone ophthalmic suspension 1% (Vexol)

**Supratarsal steroid injection**

Advanced VKC not responding to conventional therapy, especially those with cornea or limbal involvement, may be treated with supratarsal steroid injection. Both short-acting (e.g. dexamethasone) and intermediate-acting steroids (e.g. triamcinolone) appear to be equally effective, and have a similar recurrence rate. Symptoms improve after 1 to 5 days, but signs such as giant papillae and shield ulcers may take 2 to 3 weeks to resolve.

**Technique:**

Under general anaesthesia, the upper eyelid is everted, and a mixture of triamcinolone 20mg/0.5ml & betnesol 2 mg/0.5ml is injected into the subconjunctiva 1mm above the superior tarsal border with a 27-gauge needle.

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8. **Immunosuppressive agents**

Immunosuppressive agents can be considered in steroid-dependent cases. Topical cyclosporine A has been shown to be effective in treatment of AKC and VKC. It is an immunomodulator, and inhibits IL-2, T cells and eosinophils. The 2% formulation has been proven effective in many studies but lower concentrations (1%, 0.5%, 0.05%) have been tried and shown to be efficacious. Tacrolimus is not available as an eyedrop, low dose systemic tacrolimus has been reported to be effective in severe AKC, and the ointment is licensed for use in atopic dermatitis.

- Cyclosporine A 0.05% (Restasis) to 2%
- Tacrolimus (FK-506)

9. **Immunotherapy**

Immunotherapy describes the immunizing process in which increasing doses of specific antigen are given to induce increased tolerance. Multiple delivery methods are available, including sublingual, local conjunctival, and subcutaneous injections. Results with sublingual immunotherapy (SLIT) documented the clinical efficacy and safety on allergic eye symptoms, but most studies referred to rhinoconjunctivitis, with ocular symptoms as a secondary outcome. Other studies did not show a long-lasting effect.

10. **Experimental interventions**

- **Montelukast**, a leukotriene receptor antagonist, has been shown to improve VKC symptoms in children treated for asthma.


- **Anti-IgE therapy – Omalizumab** administered subcutaneously is currently approved for treatment of asthma. A study using this drug in seasonal allergic rhinitis reported improvement in ocular symptoms.


- Others have been used in animal models and found to have an inhibitory effect on antigen-induced conjunctivitis
  - Anti-ICAM-1 antibodies
  - IL-1 receptor antagonist
  - P-selectin glycoprotein ligand 1
II. Blepharoconjunctivitis (BKC)

BKC is a common but under-recognized problem in children. The condition is similar to that seen in adults but there are important differences in terms of clinical presentation and treatment.

BKC is primarily an eyelid margin disease with secondary corneal and conjunctival involvement. It is traditionally divided into anterior and posterior blepharitis although the conditions often coexist. Anterior disease involves the anterior lid margin, hair follicles and associated oil glands, whereas posterior disease is associated with meibomian gland dysfunction.

<table>
<thead>
<tr>
<th>Anterior blepharitis</th>
<th>Posterior blepharitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Inflamed eyelids</td>
<td>• Meibomian gland pouting, capping, hypertrophy or inflammation</td>
</tr>
<tr>
<td>• Lid margin telangiectasia</td>
<td>• Posterior lid margin telangiectasia</td>
</tr>
<tr>
<td>• Scales and collarettes base of lashes</td>
<td></td>
</tr>
<tr>
<td>• Madarosis</td>
<td></td>
</tr>
<tr>
<td>• Trichiasis</td>
<td></td>
</tr>
<tr>
<td>• Lid notching</td>
<td></td>
</tr>
<tr>
<td>• Meibomian gland pouting, capping, hypertrophy or inflammation</td>
<td></td>
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</table>

In addition to the above signs, chronic BKC are often associated with mild papillary or follicular hypertrophy of the palpebral conjunctiva. Acute exacerbations present with episodes of conjunctivitis, and may be accompanied by a variety of secondary corneal changes such as punctate epithelial erosions, subepithelial infiltrates, phlyctenules, marginal keratitis and ulceration. Cornea scarring and vascularization may develop. Recurrent chalazia or styes may be another presenting feature.

Important features in children:

• Age of presentation is around 6-7 years (mean 6.9 years\textsuperscript{1}, 7 years\textsuperscript{2}, 6.5 years\textsuperscript{3}, median 5.4 years\textsuperscript{4}), although there is usually a delay of 1 to 2 years between the onset of symptoms and diagnosis.

• Cornea involvement is common 81\%\textsuperscript{1}, 65\%\textsuperscript{2}, 64\%\textsuperscript{3}. However, there may be a selection bias as all the quoted studies are from tertiary referral centers which tend to see more severe disease.

• Location of cornea involvement tends to be central or paracentral rather than the classical peripheral or marginal inflammation seen in adults\textsuperscript{1}.

• Visual impairment is common. Superimposed amblyopia due to prolonged corneal opacification and/ or refractive changes (in particular astigmatism due to cornea scarring) is frequently present.

• There may be frequent exacerbations requiring prolonged steroid treatment.
Treatment strategies:

1. **Lid hygiene/ warm compresses** – using cotton wool tipped swab sticks warm water, diluted baby shampoo or special products like Blephagel or Lid Care. Modified lid hygiene using a clean fingertip or warm damp flannel to rub the eyelids at the base of lashes during showering may be more easily implemented in small children¹.

2. **Topical antibiotics** - A variety of topical antibiotics have been used including chloramphenicol 0.5%, ciprofloxacin, gentamicin, fusidic acid. *Staphylococcus aureus* or *Staphylococcus epidermis* are the most common organisms cultured form conjunctival or lid swabs taken.

3. **Topical steroids** – prednisolone acetate 1%, prednisolone 0.5%, or fluoromethadione (FML) 0.1% depending on severity. Patients should be converted to FML once the disease comes under control as it is less likely to induce secondary glaucoma.

4. **Systemic antibiotics** – Oral tetracycline has been reported to be successful, but is contraindicated in children under the age of 8 years because of its effect on dental enamel. Oral erythromycin has also been found to be effective and well tolerated, although it is unclear whether the mechanism of action is a direct effect on lipid synthesis or influence on the microflora. Recommended dosage ranged from 25% to 80% of the recommended dose for treatment of moderate infections in children (50mg/kg per day in divided doses). Treatment is usually required in the longterm but should be reduced quickly to the minimum dose required to control lid margin disease.

5. **Flaxseed oil (α-linolenic acid)** – can be considered for children who unable to tolerate or reluctant to use longterm systemic antibiotics. It is a source of omega-3 essential fatty acids which have been found to have anti-inflammatory effects and improve dry eye syndrome. In addition, they appear to have a thinning effect on meibomian secretions. The dosage recommended is 2.5ml once a day reducing to alternate days for up to 6 months³.

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III. Persistent epithelial erosions

Punctate epithelial erosions (PEEs) may cause pain, watering, photophobia and difficulty in opening eyes. Children usually present with rubbing of eyes. Vision is mildly reduced in the acute stage, but healing may be associated with scarring which can lead to astigmatism.

Common causes are:

- Trauma
- Exposure keratitis - lagophthalmos, proptosis
- Viral keratitis – especially molluscum contagiosum
- Herpetic keratitis
- Vernal keratoconjunctivitis
- Trichiasis – epiblepharon common in Asian children
  – cicatricial entropion secondary to infection or immune disease
- Dry eyes – primary (very rare in children)
  – secondary e.g. blepharokeratoconjunctivitis
- Neurotrophic keratitis
- Cornea dystrophies e.g. Reis-Buckler, Meesman or lattice dystrophies can cause painful recurrent erosions in children.
- Epidermolysis bullosa (junctional type)
- Cystinosis

Lubrication

Lubrication is the mainstay of treatment, which can be in the form of drops, gels or ointment. Artificial tears can be classified by the type of viscosity enhancing ingredients or hydrogels used in the formulation. Hydrogels are polymers that swell up in water and retain the moisture and will determine the viscosity, retention time and adhesion to the ocular surface. The following hydrogels have been used in artificial tears: Hydroxypropyl Methylcellulose (HPMC), Carboxyl Methylcellulose (CMC), Polyvinyl Alcohol (PVA), propylene glycol, carbopol, dextran, hyalouronic acid, or carbamer 940.

To increase the retention time on the eye surface, Systane uses HP-Guar which forms a “soft gel” once exposed to the eye, with increased viscosity and bioadhesive properties. 

Artificial tears such as Celluvisc and Refresh liquigel which have increase viscosity also increase retention time, but blurring occurs after instillation, lasting up to 24 minutes.

Oil containing eyedrops (see below) will replenish the lipid layer and prevent tear evaporation. This may be useful in meibomian gland dysfunction.

Tear osmolarity increases in dry eyes, and moderately hypotonic artificial tears have been show to promote ocular surface healing in dry eyes.
Preservatives are added to increase the shelf life of artificial tears. The commonly used benzalkonium chloride (BAC) can increase irritation and disease, and the newer preservatives such as GenAqua (sodium perborate) and Polyquad (Polyquaternium-1) may be preferable\(^3\). Preservative-free solutions are the best choice, but are expensive as they are dispensed in single use vials or vials that can be kept for 12 hours only once opened.

1. Carboxyl Methylcellulose (CMC)

<table>
<thead>
<tr>
<th>Product</th>
<th>Active Ingredient(s)</th>
<th>Preservative</th>
</tr>
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<tbody>
<tr>
<td>Refresh Tears</td>
<td>0.5% CMC</td>
<td>Purite</td>
</tr>
<tr>
<td>Refresh Plus</td>
<td>0.5% CMC</td>
<td>None</td>
</tr>
<tr>
<td>Refresh Liquigel</td>
<td>1% CMC</td>
<td>Purite</td>
</tr>
<tr>
<td>Refresh Celluvisc</td>
<td>1% CMC</td>
<td>None</td>
</tr>
<tr>
<td>Thera Tears</td>
<td>0.25% CMC, Hypotonic</td>
<td>None</td>
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2. Hydroxypropyl Methylcellulose (HPMC)

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<tr>
<th>Product</th>
<th>Active Ingredient(s)</th>
<th>Preservative</th>
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</thead>
<tbody>
<tr>
<td>Bion Tears</td>
<td>0.3% HPMC, 0.1% Dextran 70. (bicarbonate &amp; zinc help mucus &amp; surface cells)</td>
<td>None</td>
</tr>
<tr>
<td>Tears Naturale Forte</td>
<td>0.3% HPMC, 0.1% Dextran 70, 0.2% Glycerin</td>
<td>Polyquad</td>
</tr>
<tr>
<td>Tears Naturale II</td>
<td>0.3% HPMC, 0.1% Dextran 70</td>
<td>Polyquad</td>
</tr>
<tr>
<td>Tears Naturale Free</td>
<td>0.3% HPMC, 0.1% Dextran 70</td>
<td>None</td>
</tr>
<tr>
<td>Genteal</td>
<td>0.3% HPMC</td>
<td>GenAqua</td>
</tr>
<tr>
<td>Genteal Mild</td>
<td>0.2% HPMC</td>
<td>GenAqua</td>
</tr>
<tr>
<td>Visine Tears</td>
<td>0.2% HPMC, 0.2% Glycerin, 1% Polyethylene Glycol 400</td>
<td>Benzalkonium Chloride</td>
</tr>
<tr>
<td>Visine Pure Tears</td>
<td>0.2% HPMC, 0.2% Glycerin, 1% Polyethylene Glycol 400</td>
<td>None</td>
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</table>
3. Polyvinyl Alcohol (PVA)

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<tr>
<th>Product</th>
<th>Active Ingredient(s)</th>
<th>Preservative</th>
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</thead>
<tbody>
<tr>
<td>Murine Tears</td>
<td>0.5% Polyvinyl Alcohol, 0.6% Povidone. (has Bicarbonate)</td>
<td>Benzalkonium Chloride</td>
</tr>
<tr>
<td>Hypotears</td>
<td>1% Polyvinyl Alcohol, 1% Polyethylene Glycol 400. <strong>Hypotonic</strong></td>
<td>Benzalkonium Chloride</td>
</tr>
<tr>
<td>Akwa Tears</td>
<td>1.4% Polyvinyl Alcohol. <strong>Hypotonic</strong></td>
<td>Benzalkonium Chloride</td>
</tr>
</tbody>
</table>

4. Propylene Glycol and/or Glycerin

<table>
<thead>
<tr>
<th>Product</th>
<th>Active Ingredients(s)</th>
<th>Preservative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced Eye Relief “Environment”</td>
<td>1% Propylene Glycol, 0.3% Glycerin</td>
<td>Benzalkonium Chloride</td>
</tr>
<tr>
<td>Advanced Eye Relief “Rejuvenation”</td>
<td>0.95% Propylene Glycol</td>
<td>Benzalkonium Chloride</td>
</tr>
<tr>
<td>Advanced Eye Relief “Rejuvenation” PF</td>
<td>0.95% Propylene Glycol</td>
<td>None</td>
</tr>
<tr>
<td>Systane</td>
<td>Polyethylene Glycol 400 0.4% (lubricant),</td>
<td>Polyquad</td>
</tr>
<tr>
<td></td>
<td>Propylene Glycol 0.3% (lubricant), Hydroxypropyl Guar (Gel forming Matrix)</td>
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</tbody>
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5. Ointments and Gels

<table>
<thead>
<tr>
<th>Product</th>
<th>Active Ingredient(s)</th>
<th>Preservative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genteal Gel</td>
<td>0.3% Hydroxypropyl Methylcellulose, Carbopol 980</td>
<td>GenAqua</td>
</tr>
<tr>
<td>Refresh PM ointment</td>
<td>57.3% White Petrolatum, 42.5% Mineral Oil</td>
<td>None</td>
</tr>
<tr>
<td>Tears Naturale PM ointment</td>
<td>56.8% White Petrolatum, 42.5% Mineral Oil</td>
<td>None</td>
</tr>
<tr>
<td>Lacrilube ointment</td>
<td>White Petrolatum, Mineral Oil</td>
<td>Chlorobutanol</td>
</tr>
<tr>
<td>Advanced Eye Relief Night Time</td>
<td>White Petrolatum, Mineral Oil</td>
<td>None</td>
</tr>
</tbody>
</table>
6. Oil Containing Drops

<table>
<thead>
<tr>
<th>Product</th>
<th>Active Ingredient(s)</th>
<th>Preservative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soothe</td>
<td>Light mineral oil 1.0%, Mineral oil 4.5% (Restoryl), polysorbate-80</td>
<td>Polyhexamethylene biguanide</td>
</tr>
<tr>
<td>Refresh Endura</td>
<td>Castor oil, polysorbate-80, Carbomer 1342 &amp; Glycerin</td>
<td>None</td>
</tr>
</tbody>
</table>


IV Persistent Epithelial Defects (PED)

When dealing with a PED, the first question to ask is:

What is wrong with the microenvironment that is causing the epithelium not to heal?

Look at:

- Corneal Sensitivity
- Tear Film
- Lid Margins
- Tarsal conjunctiva
- Intraocular pressure
- Limbal stem cells

1. Corneal sensitivity

Causes of corneal anaesthesia include:

- Herpes simplex keratitis
- Trigeminal nerve damage
- Congenital – rare, either confined to the cornea only, or associated with anaesthesia in V1 and V2.
2. Tear film

Look at the tear meniscus, and tear break up time (TBUT) – non-invasive if possible but with fluorescein if no tearscope available. Severe dry eye is rare in children but can occur, and may be an indication of an underlying systemic disease.

3. Lid margins

Look for
- incongruence of lid margins
- meibomian gland dysfunction
- aberrant lashes or trichiasis

4. Tarsal conjunctiva

Look for scarring e.g. after Steven Johnson or trachoma

5. Intraocular pressure

6. Limbal stem cells

Look for aniridia or evidence of abnormal staining patterns at limbus

**Treatment options:**

1. Lubrication

See above,
In addition,
- autologous serum
- albuminate
- Healon
- Hyaluronic acid drops

2. Punctal plugs

- Dissolvable collagen plugs (lasting 7 to 10 days)
- Semipermanent silicon plugs
- Permanent punctual occlusion using thermocautery or radiofrequency needle

3. Amniotic membrane transplant

- use as patch graft to fill in defect
- use as bandage contact lens
- for treatment for tarsal conjunctival scarring
4. **Tarsorrhaphy**
   - Central
   - Lateral

5. **Botulinum toxin – induced ptosis**

6. **Treat any lid problem**
   - Tarsal eversion for trichiasis
   - Anterior lamellar repositioning for trichiasis

7. **Limbal stem cell transplant**
   - Living related
   - Cadaveric