Case 1- 61 year old female with 4 day history of am eyes being shut closed. Very itchy and sore. On Latanoprost OU. Vision no change.

Case 2- 23 year old female with a month history of sore, itchy and scratchy eyes. Has been on “lots” of different drops with little resolution. Thinks some were antibiotics. Runny nose. Vision unchanged.

Case 3- 54 year old female with sore eye. Has been on three courses antibiotic drops and also tried Visine. No help. Eye bit blurry.

Case 4- 74 year old female with 3 week history of sore, itchy eyes and eyelids. Bit blurry. On Combigan drops.
Case 5: 37 year old farmer with long standing redness, itching and blur. Has seen many doctors and only some relief. Also, stuffy nose that is worse every spring.

Case 6: 78 year old male with chronic redness and discomfort. No blur. Growing “spot” on OS. Had “scrapping” on OD in past.

Estimated Prevalence of Allergic Conjunctivitis

- Seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC) account for ~95% of all ocular allergy cases in the United States1
- More than half of allergic conjunctivitis cases are seasonal or intermittent2
- Over 41 million bottles of over-the-counter (OTC) and 4 million bottles of prescription anti-allergy ophthalmics are consumed yearly3
- ~20% population affected, of these 50% affected year round and 46% affected quality of life [2013 AAO PPP Conjunctivitis]

2013 American Academy of Ophthalmology PPP Conjunctivitis

- Allergic
  - Seasonal Allergic
  - Vernal
  - Atopic
  - Giant Papillary Conjunctivitis (also has a mechanical component)
- Mechanical/Irritative/Toxic
  - SLK
  - Contact lens related
  - Floppy eyelid
  - Giant Fornix
  - Pediculosis
  - Medication
  - Conjunctival chalasis

Allergic Response: Multiple Inflammatory Mediators

2013 American Academy of Ophthalmology PPP Conjunctivitis

- Viral
  - Adenoviral
  - HSV
  - VZV
  - Molluscom Contagiosum
- Bacterial
  - Bacterial (including gonococcal and nongonococcal)
  - Chlamydial
2013 American Academy of Ophthalmology PPP Conjunctivitis

- Immune Mediated
  - Ocular Mucous Membrane Pemphigoid
  - Graft versus host disease
  - Stevens-Johnson Syndrome
- Neoplastic
  - Sebaceous Cell Carcinoma
  - Ocular surface squamous neoplasia
  - Melanoma

Allergic (and related) Conjunctivitis
Associated/predisposing factors/natural history/clinical signs

Seasonal(Perennial) Allergic Conjunctivitis

- Environmental allergens, allergic rhinitis
- Recurrent
- Bilateral
- Conjunctival injection, chemosis, watery discharge, mild mucous discharge

Vernal Keratoconjunctivitis

- Environmental allergens
- More in hot, dry climates (e.g., Mexico, North and South America)
- Onset in childhood, males, chronic with acute, decrease over 2-20 years, 90% assos. atopic conditions such as asthma, eczema, allergic rhinitis
- Palpebral and Limbal subtypes
- Bilateral, giant papillary hypertrophy (superior/cobblestone), bullbar injection, conj scars, watery/mucoid discharge, limbal Trantas dots, corneal erosions/vascular/vernal plaque/shield ulcer

Atopic Keratoconjunctivitis

- Genetic predisposition (5-20% population; 20-40% of atopic dermatitis pts., 85% asthma, more male, peak 30-50 years)
- Environmental allergens acute episodes, Type 1 and 4 reaction
- Childhood onset, chronic with acute
- Bilateral, eczematoid blepharitis, eyelid thickening/scar/lash loss/papillary hypertrophy (inferior), conj scarring/watery/mucoid discharge, corneal neo/ulcer/scars
PEK, Associated with keratoconus/ subcap cataract/Herpes keratitis

Atopic Keratoconjunctivitis

Periocular eczema
Corneal pannus and haze
Atopic Keratoconjunctivitis

- Increasing corneal pannus
- Invading visual axis

Table: Major Differentiating Factors Between VKC and AKC

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>VKC</th>
<th>AKC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset</td>
<td>Generally presents at a younger age than AKC</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Males are affected preferentially</td>
<td>Females are predominate</td>
</tr>
<tr>
<td>Seasonal variation</td>
<td>Typically occurs during spring months</td>
<td>Generally perennial</td>
</tr>
<tr>
<td>Discharge</td>
<td>Thick mucoid discharge</td>
<td>Watery and thin discharge</td>
</tr>
<tr>
<td>Conjunctival scarring</td>
<td>Rare</td>
<td>Higher incidence of conjunctival scarring</td>
</tr>
<tr>
<td>Horner–Trantas dots</td>
<td>Not present</td>
<td>Presence of Horner–Trantas dots is common</td>
</tr>
<tr>
<td>Corneal neovascularization</td>
<td>Not present</td>
<td>Corneal neovascularization is present</td>
</tr>
<tr>
<td>Presence of eosinophils</td>
<td>Conjunctival scraping reveals eosinophils to a greater degree in VKC than in AKC</td>
<td>Presence of eosinophils is less likely</td>
</tr>
</tbody>
</table>

Giant Papillary Conjunctivitis

- Contact lens misuse, poor fit, allergy to solutions, Suture and prosthesis exposure.
- Gradual increase, type 1 and type 4 reaction
- Papillary hypertrophy (>0.3mm), superior papillary hypertrophy, mucoid discharge, lid swelling, ptosis

Superior limbic keratoconjunctivitis (SLK)

- Dysthyroid state, middle aged, female
- Subacute, wax and wane over years
- Bilateral superior bulbar injection/edema/keratinization, fine upper papillary reaction, PEK, Corneal filaments (superior)

Contact lens related keratoconjunctivitis

- Contact lens related mechanical irritation, hypoxia, preservatives
- Subacute to acute
- May take time to resolve
- Diffuse conj hyperemia, corneal neo. Punctate keratopathy, papillary hypertrophy. Limbal stem cell deficiency?
Contact lens related keratoconjunctivitis

- Contact lens wear can cause a change in corneal physiology, which can lead to epithelial, stromal, and endothelial compromise. Other complications include lens deposition, allergic conjunctivitis, giant papillary conjunctivitis, peripheral infiltrates, microbial keratitis, and neovascularization.

Floppy eyelid syndrome

- Obesity, sleep apnea, upper lid laxity, upper eyelid over lower (lid imbrication), ptosis
- Chronic irritation due to nocturnal eyelid ecropion (tarsus contact bed)
- Upper lid edema, easily everted, diffuse papillary reaction, PEK, pannus, bilateral, keratoconus associated

Floppy eyelid syndrome

- Presenting symptoms: Unilateral or bilateral chronic eye irritation and burning
- Tearing
- Ropy, mucoid discharge: usually worse in the morning
- Decreased vision, if there is an associated keratopathy
- Daytime somnolence
- Morning headaches

Giant fornix syndrome

- Elderly women(8th – 10th decade), upper lid ptosis with large fornix, mucopurulent material (waves and wanes)
- Enlarged superior fornix
- Results in a chronic staphylococcal pseudomembranous conjunctivitis that arises from a self-perpetuating infection of a nodule of protein coagulum located in the expansive upper conjunctival fornices of the elderly
- Similar to floppy eyelid
- More often unilateral

Pediculosis palpebrarum(Phthirus pubis)

- Sexually transmitted, pubic lice, alert if in children
- Blepharitis/conjunctivitis
- Uni/Bilateral follicular conjunctivitis, lice at base of lash/nits on shaft/bloody debris

Medication induced keratoconjunctivitis (Toxic)

- Glaucoma topical meds, topical antibiotics, antivirals, preservatives,
- Other irritants
- Polypharmacy, increased frequency, worsens over times
- Conjunctival injection, inferior fornix/bulbar conj follicles, eyelid erythema/dermatitis
Conjunctival chalasis
- History previous eye surgery, dry eye, redundant conj
- Chronic irritation, similar symptoms to dry eyes
- Redundant conjunctiva
- Significant but selective inflammatory markers in conjunctival chalasis, including pro-matrix metalloproteinase-9 and cytokines IL-6 and IL-1 beta (Acera et al. Ophthalmic Res 2008)

**Allergic (and related) Conjunctivitis**

**Treatment**

Seasonal Allergic Conjunctivitis
- OTC/prescription antihistamines/H1 receptor blockers
- Mast cell stabilizers
- Corticosteroids
- Lubricants/other measures
- See later

Vernal Conjunctivitis
- Adjust environment
- Topical/oral antihistamines
- Acute- topical steroids
- Cyclosporine 0.05% for keratoconjunctivitis
- Steroid injection(supratarsal)
- Over 2 years age- topical pimecrolimus/tacrolimus
- Shield ulcer- scrape plaque/topical antibiotic

Atopic Conjunctivitis
- Adjust environment
- Topical/oral antihistamines
- Acute- topical steroids
- Cyclosporine 0.05% for keratoconjunctivitis
- Steroid injection
- Over 2 years age- topical pimecrolimus/tacrolimus
- Shield ulcer- scrape plaque/topical antibiotic
- Photographs/c/o Logan et al

Giant Papillary Conjunctivitis
- Rid causative agent
- Mast cell stabilizers
- Treat aqueous deficiency, blepharitis
- Short term topical steroids
Superior limbic keratoconjunctivitis (SLK) (2013 AAO ConjunctivitisPPP)

- Treat dry eye component
- Mast cell stabilizer/topical cyclosporine
- Filamentary keratitis-topical 10% acetylcysteine/hypertonic 5% saline
- Tight upper eyelid with loose superior bulbar conj
- Surgery? Correct thyroid problems. Rare vision loss
- Keratinization of the epithelium (see the keratohyaline granules and anucleate squamous cells here), acanthosis (notice the thickening to the far right), and cellular infiltration with lymphocytes, plasma cells

Superior limbic keratoconjunctivitis (SLK)

- SLK has been treated with, mast cell stabilizers, silver nitrate or thermal cauturisation of the superior bulbar conjunctiva, pressure patching, and large diameter bandage contact lenses (BCL), topical trans-retinoic acid 0.1%, and recession or resection of the superior bulbar conjunctiva. Over 50% of patients with SLK are said to have keratoconjunctivitis sicca and upper punctal plugs have been used to treat SLK (Watson et al. BJ O 2002)
- Topical liquid nitrogen cryo (John T., Ocular surgery news, Jan 2012)

Contact lens related keratoconjunctivitis

- Hypoxia of limbal stem cells – PEK, pannus, neo
- Stop contact
- Topical steroids
- Cyclosporine 0.05%
- Orthokeratology related pseudomonas ulcer

Floppy eyelid syndrome

- Unsuccessful trials of artificial tears, vasoconstrictors, or topical steroids and antibiotics have already occurred before the correct diagnosis is made
- Taping lids shut
- Lubricants
- Upper lid horizontal shortening
- Ptosis repair
- Keratoconus associated
- Treat sleep apnea
- Rule out Mitral valve prolapse

Giant fornix syndrome

- Staph aureus treat topical antibiotics
- Treat nasolacintal obstruction/infection
- Culture given increasing rates MRESA
- *Correct ptosis
- Topical steroids, oral antibiotics, sweeping upper fornix
- Conjunctivoectomy with resection of redundant fornical conjunctiva with subconjunctival antibiotics/Nahari CR et al, Ophthal Plast Reconstr Surg 2013 Jan-Feb

Pediculosis palpebrarum (Phthirus pubis)

- Remove lice and nits
- Smother nits with erythromycin/bacitracin ointment
- yellow mercuric oxide 1%; ammoniated mercuric oxide 3%; cholinesterase inhibitors; fluorescein 20%; and 2.5% pyrethrum cream
- Treat rest of body
- Notify contacts and school
Medication induced keratoconjunctivitis (Toxic)

- Stop offending agent
- Topical steroids
- Non preserved lubricant
- Sub-epithelial fibrosis-topical steroids

Conjunctival chalasis

- Ocular lubricants
- Topical steroids
- Superficial conjunctival cauterization may be an effective treatment for mild or moderate levels of conjunctival chalasis
- ? Conjunctival resection with placement of AMT

Table 1. Comparison of Type 1 and Type 4 Hypersensitivity Reactions

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Type 1</th>
<th>Type 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue/organ</td>
<td>Intravenous</td>
<td>Endogenous tissues/organ</td>
</tr>
<tr>
<td>Time</td>
<td>Minutes</td>
<td>Days</td>
</tr>
<tr>
<td>Antibody</td>
<td>IgE</td>
<td>None</td>
</tr>
<tr>
<td>Transfer</td>
<td>None</td>
<td>T Cells</td>
</tr>
<tr>
<td>Histology</td>
<td>Eosinophils/basophils</td>
<td>Lymphocytes/monocytes</td>
</tr>
</tbody>
</table>

Table 2. Diagnostic Characteristics for the Different Forms of Allergic Conjunctivitis

<table>
<thead>
<tr>
<th>SAC</th>
<th>PAC</th>
<th>VKC</th>
<th>AKC</th>
<th>GPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>20-40</td>
<td>20-40</td>
<td>&lt;10</td>
<td>5-20 or 20-50</td>
</tr>
<tr>
<td>Sex</td>
<td>M=F</td>
<td>M=F</td>
<td>M&gt;F</td>
<td>M&gt;F</td>
</tr>
<tr>
<td>Season</td>
<td>Spring, Fall</td>
<td>Perennial</td>
<td>Spring, Fall, Perennial</td>
<td>Any</td>
</tr>
<tr>
<td>Papillae</td>
<td>Small</td>
<td>Small</td>
<td>Giant</td>
<td>Frequent</td>
</tr>
<tr>
<td>Serum IgG</td>
<td>70%</td>
<td>70%</td>
<td>Variable</td>
<td>Significant</td>
</tr>
<tr>
<td>Eosinophils in scraping</td>
<td>20%</td>
<td>20%</td>
<td>Typical</td>
<td>Typical</td>
</tr>
<tr>
<td>Goblet cells</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
<td>Reduced</td>
</tr>
</tbody>
</table>

2013 American Academy of Ophthalmology
PPP- Seasonal Allergic Conjunctivitis (SAC)

- Mild SAC can be treated with an over the counter antihistamine/vasoconstrictor agent or with the more effective second generation topical Histamine H1-receptor antagonists. Chronic use of vasoconstrictor agents can be associated with rebound vasodilation once the agent is stopped. If the condition is frequently recurrent or persistent, mast cell stabilizers can be utilized. May new medications combine antihistamine activity with mast cell stabilizing properties and can be utilized with either acute or chronic disease.

2013 American Academy of Ophthalmology
PPP- Seasonal Allergic Conjunctivitis (SAC)

- “If the symptoms are not adequately controlled, a brief course (1 or 2 weeks) of low potency topical corticosteroids can be added to the regimen. A NSAID drug, ketorolac, has also been approved by the FDA for the treatment of allergic conjunctivitis”.
- “Consultation with an allergist or dermatologist may be helpful for patients who have disease that cannot be adequately controlled with topical medications and oral antihistamines.”
- “The use of topical mast cell stabilizers can also be helpful in alleviating the symptoms of allergic rhinitis.”
### Novel Therapies

Some may be useful in future

### Therapeutic Targeting of Eosinophil Adhesion and Accumulation in Allergic Conjunctivitis (Baiula et al., Front Pharmacol. 2012;3:203)

- 

### Current practical implications

- Bimosiamose (TBC-126) blocks E-selectin-mediated leucocyte recruitment and attenuates late asthmatic reactions after allergen challenge in mild asthmatics.

- Efalizumab was approved for the treatment of moderate to severe plaque psoriasis (Frampton and Piskner, Am. J. Clin. Dermatol. 2009), but was withdrawn from the market in 2009 because of three cases of progressive multifeatral leukoencephalopathy.

- Natalizumab (Tysabri®), used in patients with multiple sclerosis is complicated by rare cases of progressive multifocal leukoencephalopathy.

- Rapastine is a selective and long-acting new drug with a strong antagonistic activity toward body histamine H1-receptors and platelet-activating factor receptor (PAF), with a proven capacity of mast cell degranulation and eosinophil chemotaxis, in vivo. Oral tablets effective in treatment of allergic rhino-conjunctivitis (Compalati E. et al., Current Medical Research and Opinion, November 2013)

### Selective glucocorticoid receptor agonists (SEGRAs)

- Glucocorticoid efficacy is due in part to the prevention of eosinophil accumulation, activation, and induction of eosinophil apoptosis, suppression of the synthesis and release of eosinophil survival factors, and stimulation of eosinophil engulfment by phagocytic cell.

- It has been hypothesized that transrepression is the key mechanism of the anti-inflammatory effects of glucocorticoids, whereas transactivation has been assumed to cause side effects.

- Glucocorticoids can either activate transcription (transactivation) by directly binding to the promoter region of target genes or by interacting with other transcription factors, such as activator protein-1, nuclear factor-kappa B, and others, or it can suppress transcription (transrepression).

- Mapracorat (also known as ZK245,186 or BOL: 303242-X) is a novel selective glucocorticoid receptor agonist that maintains a beneficial anti-inflammatory activity but seems to be less effective in transactivation, resulting in a lower potential for side effects. Studies of this SEGRA and others is ongoing (Berlin M. Expert Opin. Ther. Pat 2010).

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### Table: Ocular Therapy

<table>
<thead>
<tr>
<th>Ocular Therapy</th>
<th>Mechanism</th>
<th>Important Treatment Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihistamines</td>
<td>Histamine H1 receptor antagonists</td>
<td>(Only target histamine-mediated responses)</td>
</tr>
<tr>
<td>Ocular Mast Cell Stabilizers</td>
<td>Prevent mast cell degranulation and release of inflammatory mediators</td>
<td>(Primarily target early-phase inflammatory mediators prior to antigen exposure)</td>
</tr>
<tr>
<td>Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)</td>
<td>Inhibit activation of cyclooxygenases</td>
<td>(Do not reduce leukotriene production)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Broad-spectrum anti-inflammatory activity</td>
<td>(Potential for adverse effects, including increased OPP and cataract formation)</td>
</tr>
</tbody>
</table>

Leukotriene Antagonists

- LTs are generated by a number of cells including mast cells, eosinophils, basophils, and neutrophils. They mediate chemotaxis, vascular permeability, edema, eosinophil migration, airway constriction, and smooth muscle contraction (Samuelson et al., Science 1997). As their effect has a long time efficacy, these molecules are defined as "slow reacting substances".
- There are two different LT inhibitors/modifiers:
  - LT receptor antagonists (LTRAs; montelukast, zafirlukast, and Pranlukast).
  - 5-Lipoxygenase inhibitor of LT synthesis (zileuton).

How does it relate to ocular allergy?

- Leukotrienes play a role in the development of seasonal allergic conjunctivitis as well as the more severe forms as vernal keratoconjunctivitis and atopic keratoconjunctivitis (Leonard et al., Clin. Exp. Immunol. 2008).
- Montelukast (Singular® Merck) usage has been examined by Gane J. et al. (The Journal of Allergy and Clinical Immunology: In Practice "Leukotriene Receptor Antagonists in Allergic Eye Disease: A Systematic Review and Meta-analysis" Jan 2013.)
- Eighteen trials, using the LTRA montelukast (in Allergic Conjunctivitis only), reviewed.
- Conclusion—In SAC, LTRAs (evidence for montelukast only) are more efficacious than placebo but less efficacious than oral antihistamines, when treating patients aged 15 years or older.

The prices are 2011 U.S. from Epocrates and a few from Canada (in brackets)—but you get the idea

<table>
<thead>
<tr>
<th>Antihistamine</th>
<th>Recommended Dosage</th>
<th>Approximate Cost</th>
<th>Approximate Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011 U.S.</td>
<td></td>
<td>$32 for 30 mL</td>
<td>$14 for 30 mL</td>
</tr>
<tr>
<td>2011 Canada</td>
<td></td>
<td>$13.50 for 30 mL</td>
<td>$5.75 for 30 mL</td>
</tr>
</tbody>
</table>

So keep the costs in mind given the duration of need.

Case 1—Bacterial conjunctivitis

Case 2—Seasonal Allergic Conjunctivitis
Case 3- Iritis right eye

Case 4- Toxic conjunctivitis

Case 5- Moderate allergic conjunctivitis only responsive to 0.2% loteprednol. Eventually had cataracts requiring removal.

Case 6- Mild episcleritis. Patient happy with simple lubricants. What about the OS “spot”?

Just swabbed it and...

Thank you
- Acknowledgments:
- Katherine Huang