Allergic Conjunctivitis

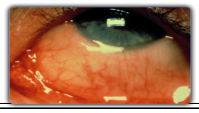
Types of Allergic Eye Disease

- **Acute allergic conditions**
  - Seasonal Allergic Conjunctivitis (Hay Fever) - SAC
  - Perennial Allergic Conjunctivitis - PAC
- **Chronic allergic conditions**
  - Vernal Conjunctivitis - VKC
  - Atopic Conjunctivitis - AKC
  - Giant Papillary Conjunctivitis - GPC

SAC and PAC *are most commonly encountered by ODs*

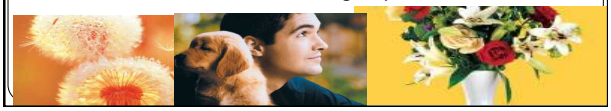
Seasonal Allergic Conjunctivitis (SAC)

- Occurs during peak allergy seasons: (spring & fall)
- Primarily caused by outdoor allergens – pollen (ragweed, mountain cedar), grasses
- Produces hallmark signs and symptoms such as:
  - itching,
  - redness,
  - chemosis,
  - tearing and
  - lid swelling



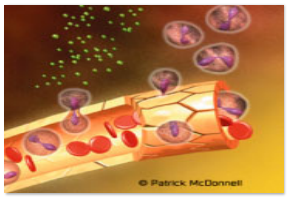
Perennial Allergic Conjunctivitis (PAC)

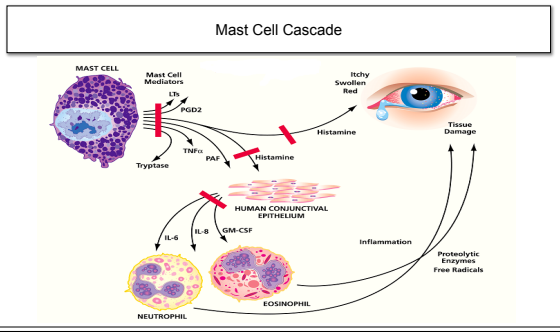
- Milder than SAC
- Occurs year round
- Primarily an indoor disease
  - -Environmental controls can be effective
- Can become more severe with higher pollen counts



Response to Histamine

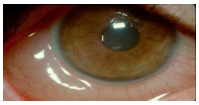
- Vasodilation
  - Erythema
- Increased vascular permeability
  - Edema
- Neural stimulation
  - Itching
  - Reflex loop increasing vascular permeability





Hallmark Clinical Signs

Hyperemia



Chemosis

Lid edema

Tearing

Treatment of Ocular Allergy

Medications:

- **Topical OTC drops**
- **Oral antihistamines** (prescription and OTC)
- **Topical NSAID drops**
- **Topical antihistamines**
- **Topical mast cell stabilizers**
- **Topical steroid drops**
- **Topical dual-action drugs** (antihistamine/mast cell stabilizers)

Vasoconstrictors

- Alpha-adrenergic agonists and are commonly used topically for the relief of conjunctival redness
  - E.g. Phenylephrine, Naphazoline, Tetrahydrozoline, Oxymetazoline
- well known and widely used
- limited duration (<2hours) limits their value when compared with the newer anti-allergy drops.
- do not interfere with the allergic reaction and do not relieve itching
- may also result in rebound hyperemia
  - E.g. Visine, Naphcon, AK-Con, Murine

Antihistamines

- Have traditionally been first line in the treatment of ocular allergy.
- H1-receptor competitive antagonists
- First generation have good safety record
  - limited duration and potency (pheniramine and antazoline). Available in OTC drops.

Antihistamines

- Newer H1 have longer duration (4-6 hrs) and are better tolerated than previous generation
  - Levocabastine (Livostin) bid-qid in patients ≥12
  - Emedastine (Emadine) bid-qid in patients >3
- FDA approved:
  - Bepotastine (Bepreve)
    - Twice day dosing for ocular itching in patients 2 or older
- Topical agents provide faster relief of ocular symptoms compared to oral agents
  - orals also have increased side-effects including dry mouth, dry eye, blurred vision, etc

Mast Cell Stabilizers

- Inhibit mast cell degranulation by interrupting normal chain of intracellular signals resulting from the crosslinking and activation by allergen.
- Several available for use in the eye:
  - cromolyn sodium 4% (Crolom)
  - nedocromil sodium 2% (Alocril)
  - Lodoxamide (Alomide)
  - Pemirolast (Alamast)

Mast Cell Stabilizers

- Cromolyn was first available
  - 1-2 drops and dosing is 4-6 times daily,
  - with a loading period of 7 days
  - has only partial inhibitory action and limited efficacy.
- Nedocromil is more potent
  - BID dosing.
- Lodoxamide
  - 2500 X more potent than cromolyn!!!
  - 1-2 drops tid-qid for up to 3 months in patients 3+
  - indicated for VKC and allergic conjunctivitis.
- Pemirolast
  - approved for QID dosing and proven to be effective in mast cell stabilization.

Dual-Action

- Trend is dual mechanism molecules
  - inhibit histamine release from mast cells
  - completely inhibits histamine binding to H1 receptors.
- Provides relief by immediate histamine receptor antagonism
  - also stabilizing future mast cell degranulation.
- Olopatadine (Patanol) is the only dual product approved for treatment of all the S&S of allergic conjunctivitis (itching, redness, lid swelling and chemosis).

Tx: NSAID's

- Mechanism of action via inhibition of the COX enzyme
  - blocks the synthesis of prostaglandins (in particular PGD2) which is known to incite significant and immediate allergic symptomatology.
- Ketorolac (Acular) proved to be effective and well tolerated at QID dosing for 2 weeks and then bid-tid as needed for itching
  - Not as effective as olopatadine (qd or bid).
- Diclofenac sodium was also shown to have some effects in controlling S&S of seasonal and VKC.

Oral Antihistamines

- Oral medications may be indicated for ocular findings associated with additional systemic symptoms such as runny nose
- Studies have shown poor efficacy in the relief of ocular findings in comparison to topical treatment
- Options Include both OTC and Rx

Oral Allergy Medications

- Oral antihistamines (pills and liquids) ease symptoms such as:
  - swelling,
  - runny nose,
  - itchy or watery eyes, and
  - hives (urticaria).
- Some oral antihistamines may cause dry mouth and drowsiness.
- Older antihistamines such as diphenhydramine (Benadryl), chlorpheniramine (Chlor-Trimeton) and clemastine (Tavist) are more likely to cause drowsiness and slow reaction time.
  - these sedating antihistamines shouldn't be taken when driving or doing other potentially dangerous activities.

1st Gen Oral Antihistamines

- Classified According to Sedation Levels:
  - Mildly Sedating
    - Brompheniramine (Generic)
    - Chlorpheniramine (ChlorTrimeton)
  - Moderately Sedating
    - Clemastine (Tavist)
  - Strongly Sedating
    - **Diphenhydramine** (Benadryl)
    - Promethazine (Phenergan)
- Most appropriate optometric use is for controlling allergic symptoms during sleep due to heavy powers of sedation
- Use at night can result in "Drug Hangover" effect

1st Generation Antihistamines - Benadryl

- Beneficial for temporary treatment of acute case of contact dermatitis
  - Topical formulas are available.
- Dosage: 50 mg TID – QID adults
  - 25 mg TID-QID kids
- Onset: within minutes with peak at 1 hour and 6-12 hour duration of action
- Pregnancy category B

1st Generation Oral Antihistamines Contraindications

- Relatively contraindicated in patients with peptic ulcer disease, prostate hypertrophy, bladder obstructions, or **narrow angles** due to the anti-cholinergic properties
- Avoid mixing with:
  - **Anti-cholinergics and adrenergic agonists**
  - **CNS depressants** (barbiturates; benzodiazepines such as Valium and Xanax)
- Elderly and those with liver dysfunction have higher risks for side effects
- Nursing mothers?
  - Follow pregnancy categories closely and work with the patients OB/ GYN

2nd Generation Oral Antihistamines

- Minimal cholinergic blocking and minimal sedation effects
  - 2nd generation antihistamines are less lipid soluble and cannot penetrate the blood brain barrier as effectively
  - Same side effects are still possible but usually much less than 1st gen drugs
- Include:
  - Fexofenadine (Allegra)
  - Loratadine (Claritin)
  - Desloratadine (Clarinex)
  - Cetirizine (Zyrtec)
  - Levocetirizine (Xyzal)

2nd Generation Antihistamines

- No major contraindications besides hypersensitivity
- Antacids may block absorption and erythromycin may increase bioavailability
- If taken in doses exceeding the recommended values, CNS side effects will likely occur
  - All may potentiate psychotropic medications to some degree
- Always use caution and consider dose adjustment in patients with kidney or renal failure
- If symptoms are not controlled with one 2nd generation antihistamine, often success can be found with another

Additional Use of Antihistamines

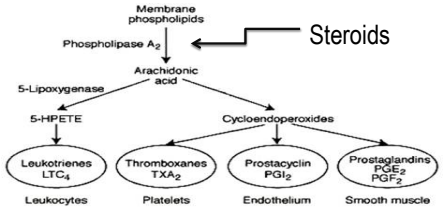
- Essential Myokymia (Eyelid Twitching)
  - Relatively mild contractions of the orbicularis muscle
    - Usually unilateral
  - Idiopathic; linked to:
    - Fatigue, stress, anxiety and caffeine
  - Findings are benign and not progressive
    - Frequently resolve in a few hours to weeks
  - Antihistamines have been clinically shown to cause relief of mild symptoms
    - Occurs by prolonging the refractory time of the orbicularis

Intranasal Medications

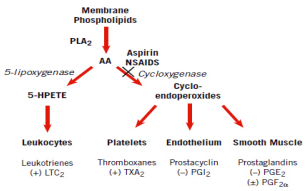
- Studies do confirm that ocular symptoms are relieved somewhat by nasal medications (corticosteroids)
- These studies show that nasal medications do give better relief of ocular symptoms than oral medications but not as beneficial as topical ophthalmic drugs
- Intra-nasal sprays plus ophthalmic drops give the more benefit and the fewer side effects than oral antihistamines

Topical NSAIDs

Steroids act at the beginning of the Arachidonic Acid Cascade.



NSAIDs

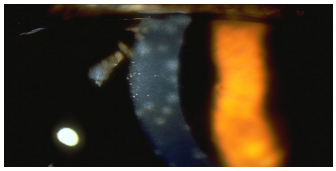


- Unlike steroids, NSAID's have only one mechanism for decreasing inflammation.
  - Inhibit the enzyme cyclooxygenase which produces prostaglandins, prostacyclins, and thromboxanes from Arachidonic Acid.

NSAID's vs. Steroids

- NSAID's are very successful at limiting inflammation systemically, but topically are less successful due to the lack of effect on the lypoxygenase pathway.

Leukotrienes attract white blood cells = Infiltrates.



Cyclooxygenase Pathway

- NSAIDs act only on inflammation through the COX pathway blocking the formation of:
  - Prostaglandins
    - Major inflammatory mediators found in virtually all tissues of the body – act locally as chemical mediators.
  - Thromboxanes
    - Promotes platelet aggregation and causes vasoconstriction
  - Prostacyclins
    - Inhibits platelet aggregation and causes vasodilation.
- There are two main enzymes involved: COX 1 and COX 2.

Cyclooxygenase Enzymes

COX 1

- Stimulated continuously by normal body physiology
  - Major player involved in secretion of mucous in the stomach and controlling blood flow to the kidneys.

COX 2

- Induced as the result of an immune response to cause higher levels of prostaglandins.

NSAIDs: Cyclooxygenase Pathway

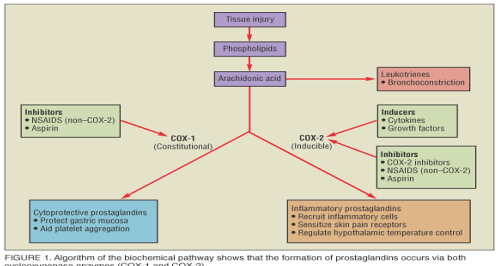


FIGURE 1. Algorithm of the biochemical pathway shows that the formation of prostaglandins occurs via both cyclooxygenase enzymes (COX-1 and COX-2).

Products of the COX 2 Pathway

- The COX 2 Pathway is responsible for the formation of inflammatory prostaglandins.
  - These prostaglandins play a role in many ocular conditions:
    - Postoperative inflammation
    - Uveitis
    - Allergic Conjunctivitis
    - Cystoid Macular Edema
  - They are also responsible for inducing miosis through sphincter contraction independent of cholinergic stimulation.

NSAID's also have other properties that make them useful in optometry.

ANALGESIC

NSAID's are primarily used for post-operative care of cataract surgery patients. However, additional uses include following FB removal or corneal abrasions as pain

NSAID's also act as antipyretics, but fevers are rarely a big concern in optometry.

Topical NSAID's

Ketorolac tromethamine 0.5% (Acular)

- Solution available from Allergan or as a generic.
- FDA Labeling for:
  - Ocular itching due to seasonal allergic conjunctivitis
  - Post-op inflammation after cataract extraction
  - Dosage: 1 drop QID
- Major Pitfall:
  - High level of stinging upon instillation

Ketorolac tromethamine 0.4% (Acular LS)

- Equal efficacy to Acular, without the sting.
- Most widely prescribed topical NSAID.
- FDA Labeling:
  - Reduction of ocular pain and discomfort following corneal refractive surgery.
    - Dosage: 1 drop QID for up to 4 days following surgery.
- Approved for patient 3 years +

~$130 for 5 ml

Diclofenac sodium 0.1% (Voltaren)

- Voltaren is indicated for the treatment of postoperative inflammation:
  - Cataract Extraction: 1 drop QID beginning 24 hours after surgery and continuing for 2 weeks following
  - Corneal Refractive Surgery: 1-2 drops of prior to surgery and 1-2 drops within 15 minutes and continued QID for up to 3 days.
- Available brand name and generic.
  - Bottle Size: 2.5 and 5 mL

Generic = $25 for 5 ml

Major stinging as well!

Bromfenac 0.07% (Prolensa)

- FDA approved in April 2013.
- 22% less medication than Bromday, but a lower pH of 7.8 making it more bioavailable.
- Solution - Available in 1.6 and 3 mL bottles from Bausch and Lomb.
- Pregnancy Category C.
- Dosage: One Drop Daily

Nepafenac 0.1% (Nevanac)

- FDA labeling is only for the treatment of pain and inflammation following cataract surgery.
- Manufactured by Alcon and sold in 3 mL bottles.
- Only NSAID that is a suspension.
- Dosage: TID beginning at one day prior to surgery and continuing for 2 weeks.

~$120 for 3 ml

Nepafenac 0.1% (Nevanac)

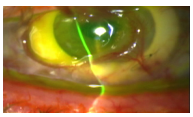
- First prodrug NSAID.
  - Hydrolyzed to amfenac in the AC.
  - This provides enhanced intraocular concentrations over the other topical NSAID's.
- Using Animal Models has been shown to inhibit prostaglandin synthesis in the retina and choroid.

Nepafenac 0.3% (Ilevro)

- FDA Approved in 2013.
  - Use for treatment of pain and inflammation associated with cataract surgery.
- Dosage: 1 Drop Daily
- Suspension that must be shaken.

Major Side Effect of Topical NSAID's

- Corneal Melt
  - Must use extreme caution in eyes with epithelial compromise.
    - NSAID's will delay wound healing (not quite to the extent as steroids, but still increase chance for infection).
    - "Melting" Ulcers will progressively take over the entire cornea.
  - Most commonly seen with generic diclofenac.
    - Has also been reported 3 times in Japan with Xibrom usage.



Side Effects of Topical NSAID's

- **Minor Side Effects:**
  - Burning and Stinging
  - Conjunctival hyperemia
  - Corneal SPK and Blurred Vision
  - Sub-epithelial Infiltrates
- **Avoiding Problems:**
  - Avoid chronic long-term use
  - Absolutely avoid in "sick" corneas…degens, Fuch's, etc

Ocular Conditions Treated with NSAID's

- Incidents Involving Corneal Induced Pain:
  - Corneal abrasions
  - Concurrently in office with Betadine for the treatment of EKC
  - Pre/Post foreign body removal
  - Post anterior stromal puncture
  - Pearls for Use:
    - Limit use to in office or less than 1 week to avoid corneal melt.
    - Stick to recommended FDA approved dosages.

Ocular Conditions Treated with NSAID's

- Active Ocular Inflammation:
  - Only prescribe if steroids are contraindicated and avoid using for more than 1 week.
  - Can be added to steroids to get a synergistic effect on inflammation.
    - Allergic conjunctivitis
    - Supplemental to steroids in treating recalcitrant uveitis
    - Supplemental to oral NSAIDs in treating scleritis
    - Treating and/or preventing inflamed pterygia and pingueculae

NSAID's and Macular Edema

- Cataract surgery results in the release of prostaglandins which breakdown the blood-aqueous barrier and move into the posterior pole.
- Once in the posterior pole they increase vascular permeability and breakdown the blood-retinal barrier resulting in macular edema.

NSAIDs and Ocular Therapy

- "Off-Label" use in preventing and treating macular edema.
- Dosage often depends on clinical picture and operating surgeon:
  - Recommended Pre-Treatment: 1-3 days in routine patients and up to 1 week in patients at risk.
  - Recommended Post-Treatment: 4 weeks for routine patients. May take 6-12 weeks in patients at risk.