Choosing the Right Agent

OFF LABEL

Front to Back

• MRSA paranoia

• Presurgical precautions
  – Health care providers (any one in household)
  – Athletes and kids
  • Gentamycin and Polytrim are great
  • Besivance is the best Fl

• Soft tissue infections like preseptal cellulitis
  – Bactrim DS

Major causes of ocular surface disease

Main Characters

• **Eosinophils**
  – are a type of white blood cell (corpuscles). They accumulate wherever allergic reactions take place. Their natural role is to defend us against parasites with toxin-filled granules.

• **Neutrophils**
  – Being highly mobile, neutrophils quickly congregate, attracted by cytokines expressed by activated endothelium, mast cells and macrophages. Uses NADPH oxidase enzyme, which produces large quantities of superoxide, a reactive oxygen species – respiratory burst

• **Cytokines**
  – Secreted proteins that bind to specific receptors (inflammation and immunity)

• **Adhesion Molecules**
  – Serve to enhance pairing between many less avid receptors and their ligands and transmit signals that direct specific effector functions
Secondary Mediators

- **Leukotrienes** - vascular permeability, sm contraction
- **Prostaglandins** - vasodilation, sm contraction, platelet activation
- **Bradykinin** - vascular permeability, sm contraction
- **Cytokines** - numerous effects incl. activation of vascular endothelium, eosinophil recruitment and activation

Secondary/Late phase mediators

- Responsible for development of severe disease
- Carry the risk of scarring
- Are self perpetuating

Dry Eye Disease: An Immune-Mediated Inflammatory Disorder

- **Lacrimal Glands**:
  - Neurogenic inflammation
  - T-cell activation
  - Cytokine secretion into tears

**Interrupted Secretomotor Nerve Impulses**

**Tears Inflame Ocular Surface**

**Cytokines**

Disrupt Neural Arc

Bell's Palsy

- Simple mechanical abrasion due to lack of tear film
- Recruitment of inflammatory factors.
  - Any amount of keratopathy involves eosinophil chemoattractant – eotaxin-1

Dry eye is not just a disease, it's a **complex, multi-factorial disorder**.
LASIK?

- Lasik decreases the superficial stromal nerves by up to 90%
- Neural feedback loop?

1. Lee et al. IOVS 2002.

Inflammation

- Decreased tear production leads to chronic inflammation on the ocular surface
  - Mechanical
  - Exposure
  - Lack of nutrients and oxygen
  - Increased irritants
- Increase expression of adhesion molecules, inflammatory cytokines, and increased activity of matrix degrading enzymes

Keratoconjunctivitis Sicca

- An autoimmune disease that involves both the lacrimal gland and ocular surface
  - Chronic inflammation
  - Lymphocyte infiltration
  - Apoptosis of ocular epithelial cells

Diabetics

- In a defect wound model in rats local application of hyaluronan improves proliferation of granulation tissue and epithelialization under diabetic conditions, thus, supporting its use in therapy of problem wounds in diabetes.


All Diabetics are at high risk of Dry Eye

- What do we use?

Hyaluronic Acid (HA) effective for dry eye

Fluorescein Tear Clearance

• Meant to differentiate the inflammatory dry eye
• Reduced clearance leads to stasis, which allows inflammatory mediators to remain in contact with ocular tissue

Tseng, Pflugfelder

ARTIFICIAL TEARS

AT are not a cure, they a treatment

Just like insulin is not a cure for diabetes

Necessary for all ocular inflammation to wash away inflammatory factors and decrease friction.

Corticosteroids

• Should be used whenever the eye looks inflammatory
  – Decreased tear production and tear clearance lead to chronic inflammation (and lid friction) on the ocular surface
• Are often needed to prevent corneal involvement
• Should be used in a pulse regime

Corticosteroids

• Will control prostaglandins and leukotrienes
• STOPS THE INFLAMMATION CASCADE
• Suppresses inflammation
• Allows for reestablishment of the neural feedback loop

How do we know that steroids work for dry eye?

Steroids and Dry Eye

• Moderate (43%) or complete (57%) relief of irritation symptoms accompanied by ↓ corneal FL staining and resolution of filamentary keratitis in 21 SS patients treated for 2 weeks with non-preserved methylprednisolone (Marsh & Pflugfelder 1999)

• Patients often have long lasting relief after 2-week pulse therapy
Steroid Efficacy

- Prednisone ≥ Loteprednol > Dexamethasone > Fluorometholone

Uveitis

Delphi Panel

- Paradigm shift in treatment

- Major Finding?

Dry Eye International Task Force: Diagnostic Recommendations

- **Level 1**
  - Mild to moderate symptoms
  - No corneal signs
  - Mild to moderate conjunctival signs

- **Level 2**
  - Moderate to severe symptoms
  - Tear film signs, visual signs
  - Mild corneal punctate staining
  - Conjunctival staining

- **Level 3**
  - Severe symptoms
  - Marked corneal punctate staining
  - Central corneal staining
  - Filamentary keratitis

- **Level 4**
  - Extremely severe symptoms/altered lifestyle
  - Severe corneal staining, erosions
  - Conjunctival scarring

Dry Eye International Task Force: Therapeutic Recommendations

- **Level 1**
  - Patient education
  - Environmental modifications
  - Control systemic medications
  - Preserved tears
  - Allergy control
  - If no improvement, add level 2 treatments

- **Level 2**
  - Unpreserved tears
  - Gels/nighttime ointments
  - Nutritional support
  - Cyclosporine
  - Sirolimus
  - Tetracyclines
  - If no improvement, add level 3 treatments

- **Level 3**
  - Punctal plugs (once inflammation is controlled)
  - If no improvement, add level 4 treatments

- **Level 4**
  - Acetylcysteine
  - Moisture goggles
  - Surgery (punctal cautery)

The Asclepius Panel Recommended Treatment Model for Dry Eye Inflammation

- Lotemax® QID (loteprednol etabonate ophthalmic suspension 0.5%)
- Artificial Tears
- Restasis® BID (cyclosporine ophthalmic emulsion) 0.05%
- Thereafter
Contacts

• Decrease corneal sensitivity
  — Decrease tear production
  — Sensory adaptation to mechanical abrasion

What’s happening in Dry Eye

• Sensory nerves may adapt to irritation by decreasing the frequency and intensity of action potentials.
• With time this elevates pain threshold, and stronger stimuli is needed to evoke corneal sensation for basal and reflex tearing
• Corneal hypoesthesia likely plays a role in the pathogenesis of tear deficiency

The Other Edge of the Sword

• Long term exposure to low levels of prostaglandins from dry eye sensitize the receptors for pain

How do we attack this?

• Indirectly go after the immune modulation in the lacrimal gland
• What if we could directly address the nerve issue in the cornea?
  — How can we do this? Pills?

NSAIDS and Dry Eye

• Initial anesthetic effect
• Long analgesic effect
• Possible cytokine modulation

Bromfenac for dry eye

• Ista drug
• Insite drug

• Great adjunctive therapy for allergic conjunctivitis
Remura?

OTHER TREATMENTS?
• What else can be done?

Bandage Contact Lens
• Not used nearly enough
• Filamentary or severe punctate keratitis
• Allows a bridge for re-epithelialization and establishment of a normal glycocalyx

Omega-3
• Women Health Study – Harvard School of Public Health
• Consumption of Omega-3s was directly related to a decreased risk of dry eye
• Omega-6 counteracts benefits of Omega-3
• Consumption of Omega-6s was correlated with increased risk of dry eye

High prevalence of bleph possibly due to poor diet

Omega-3
• Omega-3 decreases inflammation throughout the body by increasing production of specific prostaglandins that are anti-inflammatory
• It also blocks production of pro-inflammatory cytokines.
**CONCLUSIONS:**

- Dietary supplementation with omega-3 fatty acids in dry eye showed no significant effect in meibum lipid composition or aqueous tear evaporation rate. On the other hand, the average tear production and tear volume was increased in the omega-3 group as indicated by both Schirmer testing and fluorophotometry.

**Bleph Treatments?**

- Are warm compresses and lid scrubs necessary?
- Artificial tears
- Antibiotics
  - Oral or topical?
- What about the inflammation?

**Durasite alternatives?**

- Besivance for blepharitis

**Doxy**

- **Doxycycline--a role in ocular surface repair**

  - Doxycycline irreversibly inhibits corneal MMP-2 activity by chelating the metal ions that are catalytically and structurally essential.

**Corneal Irregularities**

- AT
- Steroids
- Omega 3s

**Blepharitis – Not Easy**

- Chronic
- Uncertain etiology
- Coexisting ocular disease

---

Cornea. 2011 Mar

Pilot, prospective, randomized, double-masked, placebo-controlled clinical trial of an omega-3 supplement for dry eye.
Viral Conjunctivitis

Ganciclovir Mechanism of Action

- Penetrates cell infected with the virus
- Phosphorylated within the cell to ganciclovir monophosphate by a viral thymidine kinase
  - Affinity for viral thymidine-kinase allows for specificity in its action
- Activation continues due to several cell kinases leading to formulation of ganciclovir triphosphate, which:
  - Inhibits viral DNA polymerase
  - Incorporates into viral DNA resulting in DNA chain termination and prevention of replication

Ganciclovir Ophthalmic gel

- Very effective systemically against life threatening systemic adenovirus disease
- May make patient less contagious
- May shorten course of ocular symptoms by 60%
  - Tabbara - Ganciclovir effects in adenoviral keratoconjunctivitis – 2001 ARVO

We need to be much more aggressive in treatment

Blepharitis and Contact Lens Intolerance

- Contact lens wear can induce dry eye symptoms in a patient who has a pre-existing, asymptomatic, marginally dry eye condition
  - Contact lens dry eye is classified as "evaporative" vs "tear-deficient"
- Contact lens use causes thinning of the precorneal tear film and interferes with the spread of mucin onto the cornea
- In a study by Ong, et al, ~30% of lens wearers developed some degree of meibomian gland dysfunction (MGD) over a 6 month period
- A recent study indicates that contact lens wear may be related to meibomian gland loss (determined by meibography) compared with non-lens wear

Thank You

derek.n.cunningham@gmail.com
Contact lens wear is associated with decrease of meibomian glands

- **RESULTS:** The meiboscore was significantly higher (P<0.0001) in CL wearers (mean, 1.72; 95% confidence interval, 1.47-1.96) than in the control group (mean, 0.96; 95% confidence interval, 0.73-1.19). The average meiboscore of CL wearers was similar to that of a 60- to 69-year-old age group from the normal population. A significant positive correlation was observed between the duration of CL wear and the meiboscore.

- **CONCLUSIONS:** Contact lens wear is associated with a decrease in the number of functional meibomian glands. This decrease is proportional to the duration of CL wear.

Contact Lens Intolerance

- We are very often too quick to replace solution or material when it is a clinical pathology that is the root of the intolerance

Thank You
derek.n.cunningham@gmail.com