NEW CONCEPTS IN OCULAR SURFACE DISEASE

Blair B Lonsberry, MS, OD, MEd., FAAO
Diplomate, American Board of Optometry
Professor of Optometry
Pacific University College of Optometry
blonsberry@pacificu.edu

Agenda

• What is OSD or Ocular Surface Disease
• What does OSD include?
  – Viral Conjunctivitis
  – Allergic Conjunctivitis
  – Herpes Simplex Keratitis (HSV)
  – Dry Eye Disease (DES)
  – Bacterial Conjunctivitis
  – Blepharitis and MGD

What’s Up with OSD?

• OSD presents a significant challenge to physicians
  – Differentiation
  – Diagnosis
  – Treatment
OSDs are Difficult to Tell Apart: Overlapping Signs/Symptoms

<table>
<thead>
<tr>
<th>Signs</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperemia</td>
<td>Foreign Body Sensation</td>
</tr>
<tr>
<td>Chemosis</td>
<td>Burning</td>
</tr>
<tr>
<td>Lid Swelling</td>
<td>Dry, Gritty Ocular Surface</td>
</tr>
<tr>
<td></td>
<td>Itchy Eyes</td>
</tr>
<tr>
<td></td>
<td>Photophobia</td>
</tr>
<tr>
<td></td>
<td>Tearing</td>
</tr>
</tbody>
</table>

Case

- 27 year old pharmacy student presents to the clinic on emergent basis
  - complains about red/painful eyes for the past 2 days
  - started OD then transferred to OS
  - reports a watery discharge, no itching, and is not a contact lens wearer
  - reports that others in his class have had a similar red eye
  - no seasonal, food or drug allergies
  - has taken Visine 4-5 times/day since eyes became red but hasn’t helped much

Question
Which of the following best represents your patient?
Conjunctivitis

Bacterial Conjunctivitis

Allergic Conjunctivitis

Viral Conjunctivitis

Blepharitis-conjunctivitis

---

Bacterial Conjunctivitis

---

Signs and Symptoms of Bacterial Conjunctivitis

Clinical presentation – uni- / bi-lateral

**Signs:**
- Bulbar conjunctival injection
- Purulent discharge
- Morning matting of eyelashes

**Symptoms:**
- Photophobia
- Blurred vision
- Tearing

---

---
Treatment/Management

• Topical antibiotic therapy
  – Vigamox TID for 7-10 days
  – Moxeza BID for 7 days (US only)
    – Category C
  – Zymad q 2 hours for Day 1, then BID-QID Days 2-7 (US only?)
    – Category C
  – Azasite BID for 2 days then qd for next 7-10 days (US only)
    – Category C
  – Besivance TID for 7-10 days
    – Category C
  – Tobramycin/Gentamicin QID for 7-10 days
    – Category B
  – Polytrim q3hrs (max 6x/day) for 7-10 days
    – approved to age of 2 months
    – Category C

Allergic Conjunctivitis

Prevalence of Allergic Conjunctivitis

• Allergies affect as many as 40 to 50 million Americans

• Incidence and prevalence of allergic conjunctivitis has been rising over the last 40 years
Signs and Symptoms of Allergic Conjunctivitis

Clinical presentation – bilateral

**Signs:**
- Conjunctival edema
- Conjunctival hyperemia
- Chemosis
- Lid edema
- Watery discharge

**Symptoms:**
- Itching
- Burning
- Photophobia
- Foreign body sensation
- Blurred vision

---

**Mast Cell Cascade**

---

**Treatment**

- Ocular allergy sufferers need;
  - fast relief of signs and symptoms,
  - long-lasting therapeutic effects,
  - comfortable and safe topical drugs,
  - convenient treatment regimen
- Therapeutic focus is mostly confined to the suppression of mast cells, their degranulation and the effects of histamine and other mast-cell derived mediators.
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)

Ocular Allergy Medication Options

<table>
<thead>
<tr>
<th>Levocabastine</th>
<th>LIVOSTIN®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emedastine</td>
<td>EMADINE® solution</td>
</tr>
<tr>
<td>Loteprednol</td>
<td>ALREX®</td>
</tr>
<tr>
<td>Rimexolone</td>
<td>VEXOL** suspension</td>
</tr>
<tr>
<td>Cromolyn</td>
<td>CROLOM*, MAXICROM™ solution</td>
</tr>
<tr>
<td>Lodoxamide</td>
<td>ALOMIDE® solution</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>ACULAR*</td>
</tr>
<tr>
<td>Suprofen</td>
<td>PROFENAL® solution</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>VOLTAIRE®</td>
</tr>
<tr>
<td>Azelastine</td>
<td>OPTIVAR®, LASTIN®, ZADITOR®, ALAWAY®</td>
</tr>
<tr>
<td>Ketotifen</td>
<td>ZYRTEC, CLARITIN</td>
</tr>
<tr>
<td>Olopatadine</td>
<td>PATANOL®, PATADAY</td>
</tr>
<tr>
<td>Pemirolast</td>
<td>BEPREVE</td>
</tr>
<tr>
<td>Alcaftadine</td>
<td>LASTACAFT</td>
</tr>
</tbody>
</table>

Viral Conjunctivitis

• Most common infectious keratitis presenting on emergent basis
• 62% caused by adenovirus
• Two major types:
  – Pharyngoconjunctival fever
  – Epidemic keratoconjunctivitis
Viral Conjunctivitis

- **PCF:** history of recent/current upper respiratory infection
- **EKC:** highly contagious with a history of coming in contact with someone having a red eye.
  - Adenovirus 8 common variant leading to “rule of 8’s”
    - First 8 days red eye with fine SPK
    - Next 8 days deeper focal epithelial lesions
    - Following 8 potential development of infiltrates
  - Resolution
- **RPS AdenoPlus available to use for adenoviral confirmation.**
  - Was marketed by NiCox but now back with RPS

AdenoPlus

- Have you heard about this?

Interpreting the Results

**NEGATIVE RESULT**
- Only a BLUE line appears in the control zone.
  - A negative result is indicative of an absence of Adenovirus Antigens.

**POSITIVE RESULT**
- The presence of both a BLUE line in the control zone and a RED line in the result zone indicates a positive result.
- Even if the RED line is faint in color, incomplete over the width of the test strip, or uneven in color, it must be interpreted as positive.
- A positive result indicates the presence of Adenovirus antigens.

www.nicox.com
**JOURNEY OF THE “RED EYE”**

- **“Red Eye” Protocol**
  - Patient has “Red Eye”
  - Front Office ID & trouble  with “Red Eye”
  - Patient is taken to “Red Eye” Room
  - “Red Eye” Protocol history & review
  - Tech performs AdenoPlus™ test to rule out Adenovirus
  - Dr. proceeds with evidence based treatment

**Viral Conjunctivitis: Signs and Symptoms**

- Gritty sensation
- Watery discharge
- Sticky in mornings
- Follicular response
- Chemosis
- Injection
- SPK
- Infiltrates possible
- Positive lymph nodes

- Pseudomembranes in severe cases
- Subconjunctival hemes

**Management**

- Consider the use of anti-inflammatory treatment to relieve patient symptoms and improve comfort
  - FML QID OU
  - Lotemax QID OU
    - (there is a new Lotemax gel that has a higher viscosity and increases contact time)
- EKC patients are typically very uncomfortable and would benefit from anti-inflammatory treatment
  - especially if infiltrates or pseudomembrane present
Management

• Betadine (Melton-Thomas Protocol):
  – Proparacaine
  – 4-5 drops of Betadine 5%
    • Get patient to close eye and gently roll them around
  – After one minute, lavage the eye
  – Steroid (e.g. fml/lotemax) 4 times a day for 4 days
• Alternative: Betadine swabsticks.
  – 5% Betadine solution only comes in 30 ml bottles cost $14.00.
  – Case of 200 Betadine swabsticks approx. 45 dollars.

Management

• Antivirals used in HSV keratitis are ineffective in treatment of viral conjunctivitis
  – New Update: in conversation with several colleagues, Zirgan 4-5 times/day has shown significant improvement in patients over a 7-10 time period.
• Important to stress limited contact with others, frequent hand washing, not sharing of towels, etc.
• Only commercial grade germicides will kill the virus!

Dry Eye
Prevalence of Dry Eye Disease (DED)

- Prevalence estimated from 7.4% to 33.7% depending on study quoted, how DED is defined and patient population studied
- Affects women more than men
- Increases as patient population ages
- 14.4% of patients self-report history of dry eye
- 7.8% of women aged 45 to 84 were clinically diagnosed with DED (Beaver Dam Study)
- Affect on quality of life (QOL):
  - Mild DED = psoriasis
  - Moderate DED = moderate angina
  - Severe DED = class III/IV angina or disabling hip fracture

Case

- 55 yr white female complains of fluctuating vision
  - Worse at near
  - Spends 8-10 hours/day on the computer
- Medical Hx:
  - Hypertension for 10 years
  - Joint pain
- Medications:
  - HCTZ for HTN
  - Celebrex for her joint pain

Exam Data

- PERRL
- EOM’s: FROM
- CVF: FTFD
- SLE:
  - TBUT 5 sec OD, OS
  - Positive NaFl staining and Lissamine green staining of conj and cornea
  - Decreased tear prism
Additional Testing/Questions

- Schirmer: < 5 mm of wetting in 5 minutes OD, OS
- RF and ANA: normal for patients age
- SS-A: 2.0 (normal < 1.0), SS-B: 1.9 (normal <1.0)
- Additional symptoms reported:
  - Patient experiences dry mouth and taking Salagen

- Diagnosis: Sjogren’s Syndrome

Differential Diagnosis of Dry Eye

Signs and Symptoms of Dry Eye

Signs:
- Ocular Surface Damage
  - Corneal Staining (Fluorescein and/or Rose Bengal)
  - Conjunctival Staining (Lissamine Green)
  - Decreased Tear Quantity
    - Schirmer Score
    - Phenol Red Thread Test
    - Tear Meniscus Height
  - Decreased Tear Quality
  - Tear Break Up Time

Symptoms:
- Grittiness
  - Burning
  - Irritation
  - Stringy discharge
  - Blurring of vision
  - Ocular Surface Disease Index (OSDI)
InflammaDry

• Point of care testing to measure MMP-9 levels
  – MMP-9 is an inflammatory biomarker found to be elevated in patients with dry eye
• Marketed by RPS

Treatment

• We initiated:
  – Omega-3 supplements (3-4 grams per day)
  – Recommended warm compresses and lid washes qhs
  – Testosterone cream 3% applied to upper lid bid
• Patient had significant improvement in symptoms with the use of the topical testosterone cream.
  – However, she was still symptomatic at the end of the day and she still had significant staining on her cornea and conjunctiva
  – Initiated FML tid for 1 month, restasis bid after 2 weeks
    • 2 months later patient reported further improvement in her symptoms
      • No conjunctival staining was noted and only slight SPK
      • Schirmer values improved to OD: 9 mm, OS: 10 mm

Role of Androgens?

• Recent studies have suggested that androgen deficiency may be the main cause of the meibomian gland dysfunction, tear-film instability and evaporative dry eye seen in Sjogren patients
• Transdermal testosterone 3% promotes increased tear production and meibomian gland secretion, thereby reducing dry eye symptoms (Dr. Charles Connor).
• Progesterone 0.05%/Testosterone 0.05% Ophthalmic Solution BID (available from Leiter’s Pharmacy)
SJOGREN’S SYNDROME:
OLD/NEW CLASSIFICATION

• Old:
  – 1° Sjogrens: occurs when sicca complex manifests by itself
    • no systemic disease present
  – 2° Sjogrens: occurs in association with collagen vascular
disease such as
    • RA and SLE
    • significant ocular/systemic manifestations

• New:
  – The diagnosis of SS should be given to all who fulfill the
new criteria while also diagnosing any concurrent organ-
specific or multiorgan autoimmune diseases, without
distinguishing as primary or secondary.

Diagnosis: New Criteria

• Sjogren’s International Collaborative Clinical Alliance
(SICCA) was funded by the National Institutes of Health to
develop new classification criteria for SS

• New diagnostic criteria requires at least 2 of the following 3:
  – 1) positive serum anti-SSA and/or anti-SSB or (positive
    rheumatoid factor and antinuclear antibody titer
    >1:320),
  – 2) ocular staining score >3, or
  – 3) presence of focal lymphocytic sialadenitis with a focus
    score >1 focus/4 mm2 in labial salivary gland biopsy
    samples

Ocular Surface Score (OSS)

• The ocular surface score (OSS) is the sum of:
  – 0-6 score for fluorescein staining of the
cornea and
  – 0-3 score for lissamine green staining of both
    the nasal and temporal bulbar conjunctiva,
  – yielding a total score ranging from 0-12.
Sjö Diagnostic Test

Sjö Diagnostic Test

Sjö: new diagnostic test for Sjogrens

- Novel biomarkers:
  - SP-1 (salivary gland protein-1),
  - CA-6 (carbonic anhydrase-6) and
  - PSP (parotid secretory protein).

- Traditional tests use ANA, SS-A and SS-B and RF antibodies which have significant limitations of sensitivity and/or specificity and are associated with later-stage disease.

- During studies, these novel antibodies were found in 45% of patients meeting the criteria for Sjögren's Syndrome who lacked the traditional antibodies for SS-A and SS-B.
Sjogren’s Ocular and Systemic

- Recently published article comments:
  - One or more extraglandular ocular manifestations (e.g. corneal scarring/melts, uveitis) were present in 35% of patients
  - 13% had vision threatening findings
  - Approximately 55% with a vision threatening ocular finding did not have an established diagnosis of primary SS at the time of presentation

Ocular and Systemic Morbidity in a Longitudinal Cohort of Sjögren’s Syndrome. Ophthalmology 2014

Sjogren’s Ocular and Systemic

- Recently published article comments:
  - all patients had dry eye symptoms for approximately 10.4 years before presentation
  - 42% of the patients had systemic manifestations resulting from primary SS
  - SS has been shown to be an independent risk factor for the development of non-Hodgkin’s lymphoma.

Ocular and Systemic Morbidity in a Longitudinal Cohort of Sjögren’s Syndrome. Ophthalmology 2014

Sjogren’s Ocular and Systemic

- Authors recommendation:
  - primary SS is associated with vision- and life-threatening complications
  - presence of SS needs to be explored in patients with clinically significant dry eye because dry eye precedes the occurrence of the systemic manifestations

Ocular and Systemic Morbidity in a Longitudinal Cohort of Sjögren’s Syndrome. Ophthalmology 2014
Dry Eye and Lid Disease?

• It is estimated that 67-75% of patients who have dry eye have some form of lid disease
  – it is often the most overlooked cause for dry eye symptoms

• Important to address the lids in any treatment plans for patients with dry eye

Recent Meeting: Dry Eye Summit

• Held in December 2014
  – Combination of optometrists, an ophthalmologist and industry

• Goal:
  – to find a way to encourage optometrists to look for, diagnose and manage dry eye in their patients
  – Come to a consensus on the minimum:
    • 3 questions that should be asked to identify dry eye patients
    • 3 diagnostic tests
    • 3 initial treatments

Identifying Gaps in Care: “Expert” vs Community ECP Practices

For What Percentage of Your Dry Eye Disease Patients Do You Recommend Any Treatment?

<table>
<thead>
<tr>
<th>% of ECPs</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5%</td>
<td>Experts (n = 28)</td>
</tr>
<tr>
<td>9%-10%</td>
<td>Experts (n = 28)</td>
</tr>
<tr>
<td>11%-25%</td>
<td>Experts (n = 28)</td>
</tr>
<tr>
<td>26%-50%</td>
<td>Experts (n = 28)</td>
</tr>
<tr>
<td>&gt;50%</td>
<td>Experts (n = 28)</td>
</tr>
</tbody>
</table>

Experts are much more likely to recommend treatment for dry eye patients.
Know the Risk Factors

- Disease
  - Diabetes
  - Allergies
- Contact lens wear
- Medications
  - Antihistamines/Decongestants
- Age
- Digital device use
  - Cell phones
  - Tablets
  - Computers

Consensus on Screening Questions

1. Do your eyes ever feel dry or uncomfortable?
2. Are you bothered by changes in your vision throughout the day?
3. Are you ever bothered by red eyes?
4. Do you ever use or feel the need to use drops?

Consensus on Baseline Diagnostic Options for Entry Level Dry Eye Disease

1. The lid
2. Staining
3. Tear stability
Recommendations from the Dry Eye Summit 2014

Consensus on Baseline Management

1. For all patients:
   A. Ocular lubrication
   B. Lid hygiene
   C. Nutrition
2. Topical anti-inflammatories

Treatment/Management

<table>
<thead>
<tr>
<th>DTS Severity</th>
<th>Treatment Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tier 1</td>
<td>No treatment</td>
</tr>
<tr>
<td></td>
<td>Use of hypoallergenic products</td>
</tr>
<tr>
<td></td>
<td>Prescribed lenses</td>
</tr>
<tr>
<td></td>
<td>Water intake</td>
</tr>
<tr>
<td></td>
<td>Environmental management</td>
</tr>
<tr>
<td></td>
<td>Psychological support</td>
</tr>
<tr>
<td></td>
<td>Allergy drops</td>
</tr>
<tr>
<td></td>
<td>Avoidance of drugs contributig to dry eye</td>
</tr>
<tr>
<td>Tier 2</td>
<td>Unpreserved tears</td>
</tr>
<tr>
<td></td>
<td>Steroids</td>
</tr>
<tr>
<td></td>
<td>Healing tears</td>
</tr>
<tr>
<td></td>
<td>Nutrients (fatty acids)</td>
</tr>
<tr>
<td>Tier 3</td>
<td>Tetracyclines</td>
</tr>
<tr>
<td></td>
<td>Punctal plugs</td>
</tr>
<tr>
<td>Tier 4</td>
<td>Surgery</td>
</tr>
<tr>
<td></td>
<td>Partial canthotomy</td>
</tr>
<tr>
<td></td>
<td>Syntocinoc anti-inflammatory therapy</td>
</tr>
<tr>
<td></td>
<td>Acetylcysteine</td>
</tr>
<tr>
<td></td>
<td>Oral cyclosporine</td>
</tr>
<tr>
<td></td>
<td>Contact lenses</td>
</tr>
<tr>
<td></td>
<td>Wearing goggles</td>
</tr>
</tbody>
</table>

Case

- 20 year old male presents with a red painful eye
  - complains about red/painful right eye
  - Started that morning when he woke up
  - reports a watery discharge, no itching, and is not a contact lens wearer
- SLE:
  - See attached image with NaFl stain
Herpes Simplex Keratitis: Clinical Features

- Characterized by primary outbreak and subsequent reactivation
- Primary outbreak is typically mild or subclinical
- After primary infection, the virus becomes latent in the trigeminal ganglion or cornea
- Stress, UV radiation, and hormonal changes can reactivate the virus
- Lesions are common in the immunocompromised (i.e. recent organ transplant or HIV patients)
Herpes Simplex Keratitis

- Topical:
  - Viroptic ( trifluridine) q 2h until epi healed then taper down for 10-14 days.
  - Viroptic is toxic to the cornea.
  - Zirgan ( ganciclovir) available, use 5 times a day until epi healed then 3 times for a week
- Oral acyclovir ( 2 g/day) has been reported to be as effective as topical antivirals without the toxicity
  - Valtrex ( valacyclovir)) 500 mg TID for 7-10 days
  - Famvir ( famciclovir) 250 mg TID for 7-10 days
- If stromal keratitis present, after epi defect has healed, add Pred Forte QID until inflammation reduced and then slowly taper

Prophylaxis?

- Prophylaxis of 400 mg acyclovir BID vs placebo for 1 year resulted in a lower recurrence in the treatment arm (19% vs 32%)  
  - Valtrex 500 mg qd was found to be equivalent to acyclovir BID
- Pitfalls to Prophylaxis:
  - Reduction of recurrence does not persist once drug stopped
  - Resistance????
    - van Velzen, et. al., (2013) demonstrated that long-term ACV prophylaxis predisposes to ACV-refractory disease due to the emergence of corneal ACVR HSV-1.
Dendritic ulceration before treatment with Zirgan

Cornea after treatment with Zirgan

Blepharitis

Current Prevalence of Blepharitis

- Although blepharitis may be a frequently overlooked condition in the United States, ophthalmologists and optometrists report that blepharitis is commonly seen in 37% and 47% of their patients, respectively.1,2

Blepharitis Patients’ Initial Motivation for Seeking Treatment

Differential Diagnosis of Blepharitis

Spectrum of Blepharitis

Anterior Blepharitis

Posterior Blepharitis

Mixed

Most Common

Anterior Blepharitis (MGD*)

Posterior Blepharitis

Spectrum of Blepharitis

Anterior

Mixed

Posterior

Most Common

Anterior Blepharitis (MGD*)

Posterior Blepharitis

Signs and Symptoms of Blepharitis

• Signs
  - Injected lid margin / conjunctiva
    - Telangiectasia (dilated blood vessels)
  - Swollen lid margin
  - Plugged, inflamed meibomian glands
  - Thickened meibomian gland secretion
  - Saponification
  - Lid debris

• Symptoms
  - Burning
  - Irritation
  - Foreign body sensation (FBS)
  - Itching
  - Tired eyes
  - Photophobia

Signs

• Injected lid margin / conjunctiva
  - Telangiectasia (dilated blood vessels)

• Swollen lid margin

• Plugged, inflamed meibomian glands

• Thickened meibomian gland secretion

• Saponification

• Lid debris

Symptoms

• Burning

• Irritation

• Foreign body sensation (FBS)

• Itching

• Tired eyes

• Photophobia

Physicochemical Differences in Normal vs MGD Patients

The thickened and turbid MG secretions in patients with MGD can be attributed to a more ordered lipid structure.

Increased phase transition temperature noted with MGD correlates with the more ordered lipid structure seen in the graph on the left.

"My patients will tell me if they are not happy"

**WRONG!**

- Less than 50% even saw an ECP
- Only 9% tried a different brand before dropping out

---

**CL’s and Dry Eye**

- A CL on the eye splits the tear film into pre-lens and pre-corneal layers
  - Been demonstrated that the pre-lens tear film evaporates 25% faster in CL patients
  - Reduced tear volumes results in increased tear osmolarity which is noted in dry eye patients, and increases risk of infection
- CL wearers may also be increased risk of dry secondary to age, sex, occupation, medications, allergies, etc.

---

**Treatment Goals for Blepharitis**

- Long-term control of underlying pathophysiology:
  - bacteria, inflammation and meibomian gland secretions
- Improvement of signs and symptoms
- Improve health of tear film lipid layer
  - Reduce risk of fluctuating visual acuity
- Reduce possible risk of progression to other conditions such as dry eye disease or chalazion
- Improve outcomes in surgical procedures and comfortable contact lens wear time
Treatment/Management

- Lid hygiene
- Oral doxycycline
  - 50 mg bid for 7-14 days then qd for next 6-8 weeks
- Topical azithromycin (AzaSite)
  - 1 gtt BID for 2 days then qhs for next 28 days
- Omega 3 supplements