Considering **Inflammation** in Dry Eye Disease

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We will cover....

• Dry Eye Characteristics
• Diagnostics and Treatments
• Evaporative dry eye (MGD) vs Aqueous Insufficiency???
• Inflammation basics
• MMP-9 (matrix metalloproteinase-9)
• Osmolarity
Why look for and treat Dry Eye Disease?

• It’s about VISION, and that is job number 1!
• Vision begins at the tear film
• It’s prevalent
• It’s underdiagnosed
• It’s undertreated
• Signs and symptoms don’t always match
• Better outcomes if caught early
Dry Eye Disease defined

- Dry eye is also referred to as ocular surface disease, dysfunctional tear syndrome (DTS), dry eye disease, or KCS.

- Dry eye is accompanied by **inflammation** of the ocular surface and increased **osmolarity** of the tear film.

- Dry eye is extremely **common** and is often **under diagnosed**.

- Dry eye can negatively impact vision quality and can cause **blurred vision**, **fluctuating vision**, reduced contrast sensitivity, and increased glare.

- Quality of life and daily activities can be greatly impacted by dry eye symptoms.

- Significant psychological impact
  - Patients have reported a willingness to trade years at the end of life to be free of dry eye disease.

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Symptoms of Dry Eye Disease

- Symptoms of dry eye:
  - Itching
  - Irritation
  - **Fluctuating vision**
  - Light sensitivity
  - Foreign body sensation
  - Excessive tearing

- Symptoms are often exacerbated by:
  - **Desiccating stress** caused by air conditioner drafts, fan and airplane environments
  - **Decreased blink rate** from prolonged visual concentration, increasing device use

Dry Eye Disease Risk Factors

• Age, female gender\textsuperscript{1}, menopause\textsuperscript{2-5}
• Certain medications
  • Anti-histamines, anti-psychotics, anti-depressants, and anti-hypertensives, oral contraceptives
• Autoimmune disease
  • Rheumatoid arthritis, Sjögren’s, systemic lupus erythematosus, progressive systemic sclerosis
• Contact lens wear
• LASIK and refractive surgery

Prevalence of Dry Eye Disease

<table>
<thead>
<tr>
<th>Dry Eye Category</th>
<th>Severe</th>
<th>Moderate</th>
<th>Episodic</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sjögren’s Disease</td>
<td>1,427,847</td>
<td>1,223,869</td>
<td>407,956</td>
<td>3,059,672</td>
</tr>
<tr>
<td>Post-menopausal Women</td>
<td>1,933,486</td>
<td>3,093,577</td>
<td>7,733,943</td>
<td>12,761,006</td>
</tr>
<tr>
<td>Men Over Age 65</td>
<td>518,751</td>
<td>864,585</td>
<td>1,729,169</td>
<td>3,112,505</td>
</tr>
<tr>
<td>LASIK Patients</td>
<td>4,722</td>
<td>9,444</td>
<td>141,667</td>
<td>155,833</td>
</tr>
<tr>
<td>Past LASIK Patients</td>
<td>34,027</td>
<td>68,053</td>
<td>340,266</td>
<td>442,346</td>
</tr>
<tr>
<td>Other</td>
<td>196,924</td>
<td>393,848</td>
<td>2,888,221</td>
<td>3,478,994</td>
</tr>
<tr>
<td>Total U.S.</td>
<td>4,115,757</td>
<td>5,653,377</td>
<td>13,241,222</td>
<td>23,010,355</td>
</tr>
</tbody>
</table>

Severity of Dry Eye Disease

• Gold standard for dry eye management

• April 2007, International Dry Eye Workshop (DEWS) Report – 3 year project involving clinicians and scientists with expertise in all aspects of dry eye

• The most important factor for treatment decisions to be based primarily on symptoms and signs

Patient disease severity does NOT correlate well with signs/symptoms

# DEWS Classification System

<table>
<thead>
<tr>
<th>DES grade</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signs and symptoms</td>
<td>Mild to moderate symptoms, episodic mild fatigue, no signs</td>
<td>Moderate to severe symptoms deemed “annoying,” limited activity episodic, tear film signs</td>
<td>Severe symptoms limiting activity, filamentary keratitis</td>
<td>Severe symptoms, constantly limiting activity, possible erosions, scarring</td>
</tr>
<tr>
<td>Diagnostics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjunctival staining</td>
<td>None to mild</td>
<td>None to mild/variable</td>
<td>Moderate to marked</td>
<td>Marked</td>
</tr>
<tr>
<td>Corneal staining</td>
<td>None</td>
<td>Variable</td>
<td>Central staining marked</td>
<td>Severe punctate erosions</td>
</tr>
<tr>
<td>TBUT</td>
<td>Variable</td>
<td>10 seconds or less</td>
<td>5 seconds or less</td>
<td>Immediate</td>
</tr>
<tr>
<td>Schirmer’s score (mm/5 min)</td>
<td>Variable</td>
<td>10 mm or less</td>
<td>5 mm or less</td>
<td>2 mm or less</td>
</tr>
<tr>
<td>Suggested treatment</td>
<td>Education, dietary modifi- cations, preserved artificial tears, eyelid therapy</td>
<td>Anti-inflammatories, tetracyclines, punctal plugs, unpreserved tears, topical cyclosporine 0.05%</td>
<td>Serum, bandage contact lenses, punctal occlusion</td>
<td>Systemic anti-inflammatory agents, possible lid surgery or amniotic membrane transplantation, Boston Scleral Lens</td>
</tr>
</tbody>
</table>

Dry Eye Diagnostics

No “gold standard” test; generally use clinical tests plus symptoms and patient history to diagnose.

<table>
<thead>
<tr>
<th>Physiological Property</th>
<th>Clinical Diagnostic Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tear production</td>
<td>Schirmer test</td>
</tr>
<tr>
<td>Ocular epithelial health</td>
<td>Staining with fluorescein, rose bengal or lissamine green</td>
</tr>
<tr>
<td>Tear film stability</td>
<td>Tear breakup time (TBUT)</td>
</tr>
<tr>
<td>Squamous metaplasia and goblet cell density</td>
<td>Impression cytology</td>
</tr>
<tr>
<td>Tear turnover</td>
<td>Fluoroscein clearance</td>
</tr>
<tr>
<td>Tear composition</td>
<td>Measurements of osmolarity or specific proteins, i.e. MMP-9, lactoferrin</td>
</tr>
</tbody>
</table>
Summary of Diagnostic Challenges

- Dry eye is often hidden until patients have progressed and experienced symptoms
- Dry eye symptoms overlap with other ocular surface diseases, complicating diagnosis
- Numerous clinical diagnostics exist, with no single method preferred
- Most ECPs use one or multiple tests, symptom assessment and patient history to diagnose

Case Report, initial exam

• 38 yo F, spends 6 hrs/day on CPU, Hx of Depression, Zoloft (SSRI)

• VA 20/20, -2.00 OU

• SPEED = 12, TFBUT 5 seconds, OU, ZQ 11 mm

• mild K and conj stain, Gr 1 MGD, lashes clear

• DEWS Category 2

• HOW DO WE MANAGE THIS PATIENT?
Treatment Options, how to choose?

- Artificial tears
- Compresses, Lipiflow
- Omegas
- Lid hygiene
- Steroids
- Restasis, Xiidra
- Doxycycline
Is it Evaporative or Aqueous Deficient?

- When deciding on treatment, this is usually the decision tree
- Is this the correct approach?
MGD vs ADDE, is that most important?

- In reality, the common factor is often inflammation.

- Greater levels of MMP-9 were found in tear fluid samples taken from patients with dry eye who had MGD, patients with non-SS ATD, and those with SS.

Inflammatory or not?

• **Why we need to know:**
  • inflammation breeds inflammation
  • acute response becomes chronic
  • tear film becomes toxic
  • drives our treatment decisions
  • need to break or prevent inflammatory cycle
Inflammation in Dry Eye......
what does that mean?

• tear film is disrupted (desiccating stress)

• stimulating pro-inflammatory cytokines, T cells, chemokines

• tear film becomes harmful to the eye, causing:
  • cell death (goblet, epithelial, lacrimal gland)
  • more inflammation
  • disrupts stasis of lacrimal function unit
Immunology 101

- Protects us against pathogens
- Must distinguish host vs pathogen
Immunology 101

• Immune Response:

• The reaction that occurs in response to the introduction of foreign substances. Foreign substances; microbes, cancer cells, chemical substances, …and, aberrantly to desiccating stress.
Inflammation

- complex biological response of body tissues to harmful stimuli, such as pathogens, damaged cells, or irritants

- protective response involving immune cells, blood vessels, and molecular mediators

- The function of inflammation is to eliminate the initial cause of cell injury, clear out necrotic cells and tissues damaged from the original insult and the inflammatory process, and to initiate tissue repair….this is how it SHOULD be
Inflammation

• Inflammation can be **acute** or **chronic**

• **Acute**
  • initial response
  • increased movement of plasma and leukocytes

• **Chronic**
  • progressive shift in the type of cells present at the site of inflammation
  • simultaneous destruction and healing of the tissue from the inflammatory process

• Sometimes inflammation can cause further inflammation; it can become self-perpetuating. More inflammation is created in response to the existing inflammation. **THIS IS WHAT OCCURS IN DRY EYE.**
Immunology 101

Chronic inflammation

- Long-term, months to years
- Can result from
  - Failure to eliminate whatever was causing an acute inflammation
  - Chronic irritant of low intensity that persists.
  - Autoimmune response to a self antigen - the immune system attacks healthy tissue, mistaking it for harmful pathogens THIS IS DRY EYE DISEASE
Dry Eye Inflammatory Pathway

Immediate phase

Early phase

Amplified phase

Chronic phase

Aberrant Activation\(^1,4,10\)
- MAP-K
- Jn-K
- NF-kB\(^2\): IL-1, TNF

CD147 (EMMPRIN) \(^{4,7}\)
- MMP release
- Occludin damage

ICAM regulation\(^5\)
- (down)
- CsA, steroids, doxy, azithro

Dendritic Cell activation\(^3,10\)
- Lymph Node
- Th0 → Th1, Th17

MPTP-mediated Apoptosis:
- Goblet Cell death prevented
- Epithelial Cell death prevented
- Goblet cell density improved\(^11\)
- Squamous metaplasia (IFN)

CD147 (EMMPRIN) \(^{4,7}\)
- MMP release
- Occludin damage

T1\(^1,4,10\)
- IFN
- IL1, TNF
- CCL5 (RANTES)

T17\(^1,4,10\)
- MMP-3,9
- epith injury
- Toll-Like R activ^n
- MAP-K (TKI)
- more IL-1, TNF,

Feedback Loop/Amplification\(^1\)
- TLR activ^n, IL-1, TNF, DC activ^n/IL-2

Tcell activation
- ICAM:LFA-1\(^5,9,10\)
- MHCII: TCR\(^1,4\)
- immunologic synapse → cytokine release

Laura M Periman, MD

COURTESY OF LAURA PERIMAN, MD
REFERENCES

1. Pflugfelder S and Stern M. Immunoregulation on the Ocular Surface. *OcSurf* 2009 7(2) 67-77

2. Nishiyama S et al. Cyclosporin A inhibits the early phase of NF-kB/Re1A activation induced by CD28costimulatory signaling to reduce the IL-2 expression in human peripheral T cells. International Immunopharm 2005: 699-710


Dry Eye Disease and MMP-9

• Matrix metalloproteinases (MMP) are proteolytic enzymes that are produced by stressed epithelial cells on the ocular surface. It is a gelatinase.

• MMP-9 in Tears
  • Non-specific inflammatory marker
  • Part of normal epithelial cell turnover
  • Normal range between 3-41 ng/ml
  • More sensitive diagnostic marker than clinical signs
  • Correlates with clinical exam findings
  • Ocular surface disease (dry eye) demonstrates elevated levels of MMP-9 in tears

Dry Eye Disease and MMP-9

• Increased concentrations of MMP-9 can be found in other diseases or conditions, including:

  • Ocular rosacea
  • MGD
  • Allergy
  • Corneal ulcers
  • Corneal erosions
  • CCH

Conjunctivochalasis and MMP-9
Conjunctivochalasis and MMP-9

The concentration of MMP-9 was significantly higher in the conjunctivochalasis eyes than in the healthy controls (223.4 ± 74.53 ng/mL vs. 20.32 ± 5.21 ng/mL; P < 0.001)

Tear MMP-9 levels as a marker of ocular surface inflammation in conjunctivochalasis.
Acera A1, Vecino E, Duran JA.
Importance of Detecting MMP-9

- Identifying elevated levels of MMP-9 facilitates better management of patients:
  - Presenting with signs or symptoms of dry eye
  - Having ocular surgery such as LASIK or cataract surgery

- When elevated levels of MMP-9 are not tested, confirmed, and treated prior to ocular surgery, the following complications may occur:
  - Less accurate pre-surgical measurements, worse acuity
  - Mild to severe dry eye
  - Asymptomatic dry eye becomes symptomatic, chronic dry eye
  - Epithelial ingrowth or LASIK flap slippage

Normal Levels of MMP-9

<table>
<thead>
<tr>
<th>Study</th>
<th>Normal Controls</th>
<th>Average MMP-9 Levels (ng/ml)</th>
<th>Standard Deviation (ng/ml)</th>
<th>Upper Range (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acera et al(^1)</td>
<td>18</td>
<td>23.6</td>
<td>17.4</td>
<td>41.0</td>
</tr>
<tr>
<td>Chotikavanich et al(^2)</td>
<td>16</td>
<td>8.4</td>
<td>4.7</td>
<td>13.0</td>
</tr>
<tr>
<td>Solomon et al(^3)</td>
<td>17</td>
<td>7.2</td>
<td>2.1</td>
<td>9.0</td>
</tr>
<tr>
<td>Leonardi et al(^4)</td>
<td>10</td>
<td>10.5</td>
<td>0.2</td>
<td>11.0</td>
</tr>
<tr>
<td>Lema et al(^5)</td>
<td>20</td>
<td>6.9</td>
<td>1.4</td>
<td>8.0</td>
</tr>
<tr>
<td>Honda et al(^6)</td>
<td>28</td>
<td>22.7</td>
<td>14.0</td>
<td>37.0</td>
</tr>
<tr>
<td>Markoullie et al(^7)</td>
<td>38</td>
<td>11.6</td>
<td>15.2</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Total/Avg/Range</strong></td>
<td><strong>147</strong></td>
<td><strong>12.9</strong></td>
<td>-</td>
<td><strong>41.0</strong></td>
</tr>
</tbody>
</table>

Literature meta-analysis supports that normal levels of MMP-9 (ng/ml) in human controls range from 3-41 ng/ml

MMP-9 and Dry Eye Severity

<table>
<thead>
<tr>
<th>Patient’s Dysfunctional Tear Syndrome Level</th>
<th>Average MMP-9 Level</th>
<th>Statistical Significance vs Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (n=18)</td>
<td>8.39 ng/ml</td>
<td>No</td>
</tr>
<tr>
<td>Severity Level 1 (n=15)</td>
<td>35.57 ng/ml</td>
<td>No</td>
</tr>
<tr>
<td>Severity Level 2 (n=11)</td>
<td>66.17 ng/ml</td>
<td>Yes</td>
</tr>
<tr>
<td>Severity Level 3 (n=9)</td>
<td>101.42 ng/ml</td>
<td>Yes</td>
</tr>
<tr>
<td>Severity Level 4 (n=11)</td>
<td>381.24 ng/ml</td>
<td>Yes</td>
</tr>
</tbody>
</table>

MMP-9 Levels in Two Types of Dry Eye

NL – Normal

MGD – Meibomian Gland Disease
EVAPORATIVE DRY EYE

SS – Sjögren’s Syndrome
AQUEOUS DEFICIENCY

P < 0.001 compared with normal subjects

WHETHER IT’S MGD OR AQUEOUS INSUFFICIENCY, INFLAMMATION IS THE COMMON FACTOR

MMP-9, the Path to Chronic Dry Eye Disease

Dry Eye / Elevated MMP-9
Cyclosporine and MMP-9

MMP-9 expression was evaluated by immuno-histochemistry. The mean percentage of MMP-9 expression of the conjunctival epithelial cells was significantly decreased.

MMP-9 expression was evaluated semi-quantitatively by measuring cytoplasmic staining for MMP-9.

Treatment Options

- Elevated MMP-9 may predict which patients will respond to anti-inflammatory therapy.

- Patients who test positive can be treated with one of the following: 1-3
  - Cyclosporine
  - Lifitegrast
  - Steroid
  - Azithromycin
  - Doxycycline

## InflammaDry 2011 Clinical Trial

<table>
<thead>
<tr>
<th>InflammaDry</th>
<th>N = 206</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
<td>121</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>22</td>
<td>59</td>
</tr>
<tr>
<td>Sensitivity</td>
<td></td>
<td></td>
<td>85% (121/143)</td>
</tr>
<tr>
<td>Specificity</td>
<td></td>
<td></td>
<td>94% (59/63)</td>
</tr>
<tr>
<td>Overall Agreement</td>
<td></td>
<td></td>
<td>87% (180/206)</td>
</tr>
</tbody>
</table>
InflammaDry® Limit of Detection

POSITIVE TEST RESULT
MMP-9 $\geq$ 40 ng/ml

NEGATIVE TEST RESULT
MMP-9 < 40 ng/ml

Normal levels of MMP-9 in human tears ranges from 3-41 ng/ml

InflammaDry 3rd Party Study

Matrix-Metalloproteinase-9 testing in dry eye syndrome
Messmer E.M., Lindenfels v. V., Garbe A., Kampik A.
Ludwig-Maximilians-University, Department of Ophthalmology, München, Germany

Purpose: The pathogenesis of Dry Eye Syndrome (DES) is complex. Inflammation seems to play a pivotal role to initiate and maintain the disease process. Multiple inflammatory markers, including Matrix Metalloproteinase 9 (MMP-9) have been isolated from the tear film of patients with DES.

Methods: A cohort of 101 probands and patients was evaluated by a subjective symptom questionnaire (ocular surface disease index-OSDI), break up time (BUT), conjunctival and corneal staining, Schirmer test and meibomian gland examination. 120 healthy eyes and 82 eyes fulfilling diagnostic criteria of DES underwent MMP-9 testing of the tear film by a commercially available test (InflammaDry) for detecting MMP-9 levels > 40ng/ml.

Results: The MMP-9 tear test showed a significant difference between healthy eyes and eyes with DES (p< 0.001). It correlated well with subjective symptoms evaluated by OSDI (p=0.001), BUT (p< 0.001), Schirmer test (p< 0.001), conjunctival (p< 0.001) as well as corneal staining (p=0.002). Moreover, it correlated with the number of obstructed meibomian ducts (p< 0.001) and a pathologic meibomian gland secretion (p< 0.001). It was significantly increased in female patients (p< 0.001), patients with obvious signs of ocular surface inflammation (p=0.003), autoimmune disease, especially Sjögren-Syndrome (p< 0.001), and thyroid disease (p=0.009).

Conclusions: MMP-9-testing in DES is a valuable new diagnostic tool. It correlates well with other dry eye tests. It is especially helpful to identify patients with ocular surface inflammation and autoimmune disease and may facilitate the decision to institute anti-inflammatory treatment in these patients.
InflammaDry 2012-13 Clinical Trial

- InflammaDry FDA Study 2012-2013
- Prospective, multicenter clinical trial
- 237 symptomatic patients enrolled
Clinical Performance Results

<table>
<thead>
<tr>
<th>N=237</th>
<th>Clinical Assessment</th>
<th>Positive % Agreement</th>
<th>Negative % Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OSDI** + TBUT + Schirmer + Staining</td>
<td>95% Confidence Interval</td>
<td>95% Confidence Interval</td>
</tr>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>127</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>30</td>
<td>78</td>
</tr>
<tr>
<td>InflammaDry Results with OSDI</td>
<td>Positive</td>
<td>126</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>20</td>
<td>88</td>
</tr>
<tr>
<td>InflammaDry Results without OSDI</td>
<td>Positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

** 11 Patients were assessed to be positive for mild dry eye based on the OSDI (OSDI ≥ 13) without any associated positive objective test results.
Clinical Performance Results

Performance without OSDI as a criteria for mild disease

- Positive Agreement 86%
- Negative Agreement 97%

Performance with OSDI as a criteria for mild disease

- Positive Agreement 81%
- Negative Agreement 98%
Key Clinical Results

• N=237 symptomatic patients
  • 61% (145/237) confirmed dry eye by TBUT, Schirmer, or staining (+/- OSDI)
    • Of the 61% confirmed dry eye, InflammaDry was positive 81%-86% (125/145-156) of the time
    • Of all symptomatic patients, InflammaDry was positive 53% (125/237) of the time (SIGN AND SYMPTOM DISCONNECT)
  • 39% (80/237) confirmed negative by TBUT, Schirmer, and staining (+/- OSDI)
    • Of the 39% (80/237) confirmed negative, InflammaDry was also negative 97%-98% of the time
**Dry Eye Disease Testing Methods**

<table>
<thead>
<tr>
<th>Test</th>
<th>Positive Agreement (Sensitivity)</th>
<th>Negative Agreement (Specificity)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>InflammaDry</strong></td>
<td>81-85%</td>
<td>94-98%</td>
</tr>
<tr>
<td>Schirmer Tear Test</td>
<td>42%</td>
<td>76%</td>
</tr>
<tr>
<td>Tear Break Up Time (T-BUT)</td>
<td>92%</td>
<td>17%</td>
</tr>
<tr>
<td>Corneal Staining</td>
<td>63%</td>
<td>89%</td>
</tr>
<tr>
<td>TearLab Osmolarity System</td>
<td>64-90%</td>
<td>71-92%</td>
</tr>
<tr>
<td>Questionnaire</td>
<td>89%</td>
<td>72%</td>
</tr>
</tbody>
</table>

InflammaDry Product Overview

• Detects elevated levels of MMP-9 in tear fluid

• Rapid: 10 minute results

• Easy to use: can be performed by a nurse or technician

• In-office: point-of-care immunoassay test aids in diagnosis at the time of office visit

• Low cost: no additional equipment required
InflammaDry Test Kit Contents

Kit includes

1 foil pouch containing a sterile sample collector

1 foil pouch containing a test cassette

1 buffer vial
InflammaDry 4-Step Process

Step 1 - Collect Sample
Gently dab the sample collector in 6-8 locations on the palpebral conjunctiva, until the fleece glistens, to collect a tear sample.

Step 2 - Assemble Test
Snap the sample collector into the test cassette and press firmly where indicated. A double-click means the test is properly assembled.

Step 3 - Run Test
Immerse the absorbant tip into the provided buffer vial for 20 seconds. Replace the cap and lay the test flat on a horizontal surface.

Step 4 - Read Results
After 10 minutes, read the test results.

- RED + BLUE = POSITIVE
- BLUE = NEGATIVE

* Release the lid after every 2-3 dabs. Allow the sampling fleece to rest along the conjunctiva for 5 seconds.
Tips for Successful Use

• The opened test cassette should be used within one hour

• Wait the entire 10 minutes of development time before interpreting the results

• InflammaDry performance depends on the antigen load in the specimen zone and may not correlate with clinical signs and symptoms

• Inadequate specimen collection may yield false negative results
Tips for Successful Use

• Reduce false negatives by:
  • Dabbing, saturating, in multiple locations along the conjunctiva
  • Releasing the lid after every 2-3 dabs
  • Make sure the collector turns pink
  • Press to double-click to allow specimen transfer
  • Reconnect the cap while the test is developing
  • Reading any form of a line, whether light or broken, as a positive
  • Waiting at least 2 hours after any topical therapies are applied to the eye as this may dilute MMP-9

• Reduce false positives by:
  • Not scraping the conjunctiva; gently dab
Reimbursement Strategy

CPT Code 83516 – Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; qualitative or semiquantitative, multiple step method

$15.46

Supportive letter from ASCRS, Cornea Society, and Vanguard Ophthalmology Society
MMP-9 limitations

- non-specific
- more than one pathway, misses TH1! (IFN-gamma)
- no absolute values
- sample can be hard to obtain
- results can be hard to interpret
Case Report, initial exam

- 38 yo F, spends 6 hrs/day on CPU, Hx of Depression, Zoloft (SSRI)
- VA 20/20, -2.00 OU
- **SPEED = 12, TFBUT 5 seconds, MMP-9 mild +, OU, ZQ 11 mm**
- mild K and conj stain, Gr 1 MGD, lashes clear
- Tx: Restasis (or Xiidra), omegas (MMP9)
- compresses (MGD)
- AT at work, qid (TFBUT, ZQ)
Case Report, Day 30

- **SPEED = 7, TFBUT 7 seconds, MMP-9 NEGATIVE OU, ZQ 12 mm**

- mild K and conj stain, Gr 1 MGD, lashes clear

- Tx: Continue Restasis or Xiidra

- TEAR QUALITY IS GOOD, INFLAMMATION IS GONE, VOLUME STILL LOW

- **ADD PUNCTAL PLUGS**

MAKE SENSE??
What about TH1 pathway?

How can we know?
TH1 Pathway.....what to look for

- IFN-g causes MPTP-mediated apoptosis (Mitochondrial Permeability Transition pore)
  - Goblet cell death
  - Compromised mucin layer
  - Hydrophobic tear spread
  - Lissamine green staining
  - LWE (goblet cell dense)
  - Hyperkeratinized LOM
New Inflammation Study

“Tear Interferon-Gamma as a Biomarker for Evaporative Dry Eye Disease”

Conclusions:
Tear hyperosmolarity is specifically associated with higher levels of the proinflammatory cytokine IFN-gamma, which correlate with key clinical parameters of DED. The calculated effect size (0.8) suggests that this assay has diagnostic power as a biomarker for evaporative DED.
IFN-gamma and osmolarity

![Graph showing the ratio of tear IFN-γ level to average cytokine level for two study groups: Normo-osmolar and Hyper-osmolar. There is a significant difference marked by an asterisk (*) between the two groups.](image-url)
Tear Osmolarity

**Normal**
- Between 280-295 mOsm/L\(^1\)

**Hyperosmolar**
- **Central pathophysiologic mechanism** for all forms of DED
- Causes **inflammation and apoptosis** & reduces the ability of mucins to lubricate
- Leads to a **breakdown of homeostatic control** causing tear film instability
- 308 mOsm/L is a highly sensitive cut-off point that delineates a normal from a mild/moderate dry eye population\(^2\)
- **Inter-eye difference = hallmark of DED** ( > 8 mOsms/L between eyes)
- **Unstable tear film causes inter-eye differences**\(^2\)

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\(^2\)Lemp MA et al., Am J Ophthalmol. 2011 May;151(5):792-798
Tear Osmolarity

The **MAXIMUM** of the two eyes:

Tears higher than 300 mOsm/L demonstrate loss of homeostasis and likely become pathogenic > 308

The **DIFFERENCE** b/w two eyes:

A difference of > 8 mOsm/L is a hallmark of tear instability
Tear Osmolarity

**Advancing dry eye disease causes:**

- Increasing osmolarity
- Asymmetry of findings

Tear Osmolarity

**Pro’s**
- Easy to administer
- Quick results

**Con’s**
- Cost of unit
- Cost of disposables
- Variability of testing
Tear Osmolarity

Research to support: May 2011

- **TearLab (Lemp, et al) properly identified (n=314):**
  - 88% of normal subjects
  - 75% of subjects who had mild-or-moderate dry eye disease
  - 95% of subjects who had severe dry eye disease
My Current Dry Eye Protocol (evolving)

- Screen all patients 10 and over, or any patient with dry eye complaints in history, all contact lens wearers
- Staff screens with SPEED questionnaire and Phenol Red Thread test
- If SPEED 7 or more, or thread test 15 mm or less, staff runs Inflammadry or osmolarity before I see the patient. They use a marker and put the patients initials and test time on the test.
- If the test is negative, look for LG, LWE, aberrant LOM, uneven tear film distribution. If present, likely there is inflammation.
- If inflammation present, prescribe lifitegrast or cyclosporine, NPAT aid, omegas
- If MGD is present, add warm compresses, LF, blink exercises
- At 1 month follow up, if negative for MMP-9 or less inflammation, but tear volume is still low, then consider punctal plugs.
- All of these patients are stained with LG and FL (not Fluress), and wait 3 minutes to eval K stain. TFBUT can be looked at right away.
Is it Evaporative or Aqueous Deficient?

- I recommend thinking in terms of whether or not CHRONIC inflammation is present.

- Address inflammation first, then go after the underlying clause.

Thank you!

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