Dry Eye Disease: Clinical Pearls and Practical Applications of New Technologies

Mile Brujic, OD, FAAO
Disclosure

Unfortunately, the speaker has no financial or proprietary interest in any of the products that are mentioned.

Co-Owner Optometric Insights with Dr. Dave Kading

I have received honoraria in the past 2 years for speaking, writing, participating in an advisory capacity or research from: ABB Optical, Akorn, Alcon Laboratories, Allergan, Art Optical, Bausch + Lomb Health, Contamac, CooperVision, CSEye, Euclid, Eyevance, Johnson & Johnson Vision Care, Luneau, Novartis, Oculus, Optovue, Sight Sciences, Sun Pharma, Tangible Science, TelScreen, Thea, TruForm Optics, Valley Contax, Visionary Optics, VMax Vision, Walman Optical, Weave, Zeiss and ZeaVision.
1) DEWS Report (2007)
2) DEWS II Report (2017)
3) International Workshop on Meibomian Gland Dysfunction
4) International Workshop on Contact Lens Discomfort
Diagnosis
Collarettes at base of lashes
Wratten #12 filter  Fluorescein strip
TBUT - Normal range
(best viewed with fluorescein)

> 10 seconds
Lissamine Green staining
Fluorescein staining
Tear Film Break Up
Lissamine green is viewed best at low light levels
Lid Wiper Epitheliopathy

80% of symptomatic CL wearers
13% of asymptomatic CL wearers
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<th>Horizontal length of staining</th>
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Most common form of MGD – Non obvious
Meiboscale

Area of Loss

- Degree 0: ≈0%
- Degree 1: ≤25%
- Degree 2: 26% - 50%
- Degree 3: 51% - 75%
- Degree 4: >75%

2012 © Dr. Heiko Pult – Optometry & Vision Research, Germany www.heiko-pult.de
Images compliments of Dave Kading, OD, FAAO
InflammaDry

- 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) test
- Low cost – no additional equipment required
- One time use – disposable
- Accurate – high sensitivity and specificity

InflammaDry is CE Marked and commercially available in Europe. At this time InflammaDry is pending 510(k) review by FDA and is not commercially available in the U.S.
How to Use InflammaDry: Four-step Process

1. Gently dab the Sample Collector in 6-8 locations on the palpebral conjunctiva (lower eyelid) to collect a tear sample. Do not use a dragging motion.

2. Snap the sample collector into the test cassette and press firmly where indicated.

3. Dip the test cassette into the provided buffer vial for 20 seconds. Replace the cap.

4. Read the results: 2 lines (1 red, 1 blue) = positive, 1 line (blue) = negative
Making Matrix Metalloproteinase-9 Levels More Meaningful
Mile Brujic, OD, FAAO, David Kading, OD, FAAO

Introduction
Dry eye, and more broadly ocular surface disease, is a complex yet intriguing condition. In this condition, we know there are a number of changes that occur to the glands. These changes affect the quality of tears as well as cause chronic changes to occur to the ocular surface that the tear film appears. These changes and environmental changes can affect both comfort and visual quality of both contact lens and also non-contact lens wearers.

There are several Inflama Dry markers that are increased in the tear film at approximately 50% of dry eye patients. Chotikavanich et al showed that MMP-9 levels increase with increasing severity of dry eye disease. A new point of care diagnostic technology that detects an elevated matrix metalloproteinase-9 (MMP-9) in the tear film is becoming an increasingly utilized test in eye care practice to help manage dry eye patients and contact lens wearers experiencing discomfort with their lenses.

It is a qualitative test that exhibits a red result line indicative of a positive result when the MMP-9 concentration in the tear is 40 ng/mL or higher. Although this gives us important qualitative information on the concentration of MMP-9 in the tear film, the signal strength of the red result line is directly proportional to the concentration of MMP-9 in the tears and can be used to estimate the relative amount of MMP-9 present. We have seen this clinically and we use it as a gauge of how our treatment is influencing the MMP-9 levels.

While the test cannot quantitate the exact level of MMP-9 in the tear film, the test proposes a semi-quantitative method of grading the intensity of the red test result line signal to assist clinicians in monitoring the success or failure of treatments with their patients.

Methods
Contrived samples of differing concentrations of MMP-9 were created and tested using the Inflama Dry test to produce positive results of varying strengths. The following concentrations of MMP-9 were tested:
- 8 ng/mL
- 34 ng/mL
- 66 ng/mL
- 101 ng/mL
- 381 ng/mL

Based on the varied intensity of the result lines, a proposed signal strength classification was developed.

Results
The test result signal intensity was found to increase proportionally to the increasing concentration of MMP-9 present in the sample. This linear relationship allowed for the grading of the signal strength. A proposed signal strength classification was developed into one of five categories:
- Negative (8 ng/mL): no red result line is present and the level of MMP-9 is below 40 ng/mL
- Trace positive (34 ng/mL): the red result line is just detectable. This is at the lower limit of the Inflama Dry test
- Weak positive (66 ng/mL): the red result line is a faint signal but stronger than the trace positive classification
- Positive (101 ng/mL): this red result line is relatively solid and easily visible
- Strong positive (381 ng/mL): this red result line is a strong signal and may appear vibrant

Discussion
Understanding the relative concentration of MMP-9 levels in the tear film facilitates a more robust understanding of the dry eye disease state as well as enhancing clinical decisions. Prior to this proposed classification system, the test simply provided a positive or negative result depending on whether the red result line was present or absent. This essentially limits the presence of either greater or less than 40 ng/mL of MMP-9 in the tears. Thus, if treating a patient for dry eye, improvements in MMP-9 measurements wouldn’t be appreciated unless the levels went from a positive to a negative.

There may be improvements in MMP-9 levels during treatment that can be graded by the intensity of the red line result. Although this doesn’t quantify the absolute concentration, it does provide perspective on any additional efforts to follow over time to demonstrate the success or failure of treatment. The concentrations were placed right beside the categories proposed above as a gauge to the approximate concentration. It is ying that, it is impossible to infer the concentration of MMP-9 to that level of accuracy based on the subjective grading scale presented here.

What was also interesting is that although the published minimum detected threshold of the Inflama Dry test is 40 ng/mL, a trace positive was actually detected at 34 ng/mL. The approach of interpreting a linear-quadratic titration result acts the clinician with additional information. This classification system provides additional tools to use the signal strength from a contemporary point of care test to guide the treatment of dry eye patients and those with contact lens comfort issues.

References

Special Thanks
To RPS Diagnostic for providing support for this poster.
Signal Strength

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InflammaDry Clinical Trial

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<td></td>
<td>+</td>
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<td></td>
<td>−</td>
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<tr>
<td>+</td>
<td>121</td>
</tr>
<tr>
<td>−</td>
<td>22</td>
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- **Sensitivity**: 85% (121/143)
- **Specificity**: 94% (59/63)
- **Overall Agreement**: 87% (180/206)
Treatment
Provide Relief
+
Improve function
Lacriserts dissolve in 24 hours
DEBS - a unification theory for dry eye and blepharitis

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Henry D Perry2
1BlephEx, LLC, Ajavon, KY, USA
2Department of Ophthalmology, Nassau University Medical Center, Hofstra University School of Medicine, East Meadow, NY, USA

Abstract: For many years, blepharitis and dry eye disease have been thought to be two distinct diseases, and evaporative dry eye distinct from aqueous insufficiency. In this treatise, we propose a new way of looking at dry eye, both evaporative and insufficiency, as the natural sequelae of decades of chronic blepharitis. Dry eye is simply the late form and late manifestation of one disease, blepharitis. We suggest the use of a new term in describing this one chronic disease, namely dry eye blepharitis syndrome (DEBS). Bacteria colonize the lid margin within a structure known as a biofilm. The biofilm allows for population densities that initiate quorum-sensing gene activation. These newly activated gene products consist of inflammatory virulence factors, such as exotoxins, cytolytic toxins, and super-antigens, which are then present for the rest of the patient’s life. The biofilm never goes away; it only thickens with age, producing increasing quantities of bacterial virulence factors, and thus, increasing inflammation. These virulence factors are likely the culprits that first cause follicular inflammation, then meibomian gland dysfunction, aqueous insufficiency, and finally, after many decades, lid destruction. We suggest that there are four stages of DEBS which correlate with the clinical manifestations of folliculitis, meibomitis, laceralitis, and finally lid structure damage evidenced by entropion, ectropion, and floppy eyelid syndrome. When one fully understands the structure and location of the glands within the lid, it becomes easy to understand this staged disease process. The longer a gland can resist the relentless encroachment of the invading biofilm, the longer it can maintain normal function. The stages depend purely on anatomy and years of biofilm presence. Dry eye now becomes a very easy disease to understand. We feel that dry eye should be treated and prevented by early and routine biofilm removal through electromechanical lid margin debridement.

Keywords: biofilm, quorum-sensing gene activation, Demodex, MGD, meibomian gland disease, aqueous insufficiency

Introduction

In 1684, Antonie van Leeuwenhoek presented to the Royal Society of London and commented on the number of “animicules” noted within the scurf of a man’s teeth. This is the first known microscopic observation of a biofilm. For over 300 years, little was known about biofilms, and research was uncommon. Biofilm implications in all of human disease were vastly underappreciated. In the past 20 years, however, biofilm research has burgeoned, with complicated but fascinating interactions between bacteria, host, and their environment now being revealed. In a similar vein, the term “blepharitis” first appears in the literature in the 1800s, but like biofilm research, little progress was made over the subsequent 100+ years in terms of understanding or treating this disease. While we have made some strides since the days of “Great German Eye Water” to treat “weak or inflamed eyes”, blepharitis remains a poorly defined disease, with the use of confusing and inaccurate terminology and considerable
Rynerson Theory of DEBS

Stage 1
Lash Follicles

Stage 2
Meibomian Glands
Lash Follicles

Decades

Time in

Inflammation damage

Bacterial virulence factors

Gene activation

Quorum sensing

Increased densities

Biofilm

Bacterial Survival
MICROBLEPHAROEXFOLIATION (MBE)
Clinical Effectiveness of Lid Debridement with BlephEx Treatment

Daniel Mulder, Kirsti Kyser, Bonnie Rosenberg, Charles Connor, Christopher Choat, Srihari Narayanan
University of the Incarnate Word, Rosenberg School of Optometry, San Antonio, Texas

ABSTRACT

Purpose: Eyelid disease is a common cause of evaporative dry eye. Lid scrubs and warm compresses done consistently will address this problem but poor compliance makes an office based procedure desirable. Khodadoust found the debridement scaling of the lower lid margin provides statistically significant symptom relief and improvement in the meibomian gland function. The BlephEx provides a method of accomplishing lid debridement without using a surgical instrument. This study compares signs and symptoms before and after BlephEx treatment.

Methods: Twenty subjects all with MG dysfunction were examined at baseline using a biomicroscope using the Efron Scale for grading. Subjects also had a TBUT and OSDI performed. The treatment was given to all subjects twice a week for 6 weeks and a TBUT was performed at 4 weeks later all testing was repeated. Data was analyzed by a t-test with post hoc test for significance.

Results: Subjects TBUT improved from 3.3±1.3 to 5.47±1.3 p<0.05. Blepharitis on the Efron scale improved from 1.24±0.56 to 0.57±0.54 p=0.02. MG dysfunction also dramatically improved from 1.65±0.5 to 0.76±0.54 p=0.02. Symptoms also improved based on the OSDI which went from 42.39±1.44 to 29.31±1.44 p=0.00.

Conclusions: This study suggests BlephEx is a viable alternative to lid scrubs and warm compresses. Statistically significant improvement was observed in signs and symptoms of the subjects treated. Eyelid function improved based on TBUT increase, reduced inflammation and enhanced MG function. Subjects were 50% less symptomatic after treatment. BlephEx appears to be a reasonable clinical approach for use in non-compliant MG dysfunction patients.

BACKGROUND

Rynerson introduced a new instrument in 2014 that aims at reducing the effects of blepharitis. The minimal invasiveness of the instrument makes it ideal for use by optometrists.

This study examines changes in the signs and symptoms of the ocular surface before and after treatment with BlephEx.

METHOD

20 subjects with MGD and dry eye symptoms participated in a prospective randomized study.

All subjects underwent an initial baseline examination.

All subjects then received the BlephEx treatment according to the manufacturer's directions.

Outcome measures obtained at baseline and 4 weeks post-treatment included:

- Biomicroscope examination using the Efron Grading Scale to grade MGD and Blepharitis severity
- Ocular Surface Disease Index (OSDI)
- Tear Break-Up Time

Data was analyzed by a t-test with post hoc test for significance.

RESULTS

- TBUTS significantly improved 4 weeks after treatment (p= 0.05)
- Blepharitis on the Efron Scale significantly improved 4 weeks after treatment (p=0.01)
- MG Dysfunction drastically improved 4 weeks after treatment (p=0.01)
- Symptoms also improved based on the OSDI 4 weeks after treatment (p=0.01)

CONCLUSIONS

- BlephEx is a viable alternative to the conventional treatment (lid scrubs and warm compresses) for blepharitis
- Statistically significant improvement in signs & symptoms 4 weeks after treatment
- Increased TBUT, decreased inflammation, and increase in MG function after treatment
- Subjects were 50% less symptomatic after treatment
59% of symptomatic CL patients were converted to asymptomatic after just one treatment.
Reduction in inflammatory marker matrix metalloproteinase-9 following lid debridement with BlephEx

Charles G Connor; Srihari Narayanan; William Miller

Investigative Ophthalmology & Visual Science June 2017, Vol.58, 498. doi:

Abstract

Purpose: Meibomian Gland Disease (MGD) is a common cause of evaporative dry eye. Lid scrubs and warm compresses can address this problem but poor compliance makes an office based procedure desirable. Korb found the debridement-scaling of the lower lid margin provides statistically significant symptom relief and improvement in MG function. The BlephEx provides a method of accomplishing lid debridement without using a surgical instrument. Ocular surface inflammation is well documented in dry eye patients. The RPS InflammaDry recognizes elevated levels of MMP-9, an inflammatory marker that is consistently
Ten MGD patients with evaporative dry eye and tested positive with InflammaDry
- OSDI, NIBUT, meibography and InflammaDry were measured before and after BlephEx treatment (4 week post treatment)
- OSDI – 26 (pre-treat) and 10.66 (post-treat)
- NIBUT – 6.99 (pre-treat) and 9.53 (post-treat)
- Meibography – no change
- InflammaDry – positive (pre-treat) and negative (post-treat)
Hypochlorous Acid

- Pure hypochlorous acid (HOCl) released from neutrophils
- Essential part of body’s immune response
- In the body, Hypochlorous Acid:
  - Kills microorganisms
  - Neutralizes inflammatory toxins released from pathogens
  - Helps suppress the body’s inflammatory response
  - Prevents biofilm formation
Hypochlorous Acid

- Avenova (0.01%)
- HyClear (0.01%)
- HypoChlor (0.02%)
- Theratears Sterilid Antimicrobial Eyelid Cleanser (0.01%)
- Bruder Hygienic Eyelid Solution (0.02%)
- Heyedrate Lid and Lash Cleanser (0.015%)
NuLids Works

- The NuLids Starter Kit includes a rechargeable cordless handpiece, one charger plug and charger cord, and an initial 30-day supply of NuLids Daily Disposable Soft Tips

- Before each treatment, a new sterile Soft Tip is attached to the handpiece

- A small amount of lubricating gel or cleaner is applied to the edge of the Soft Tip [i.e. ZocuShield Gel/Systane /Hypochlorous acid]

- The handpiece is then powered on and the Soft Tip begins oscillating back and forth in a 15° arc pattern

- The Soft Tip is then gently placed on the eyelid margin and smoothly moved back and forth across the entire lid margin for approximately 30 seconds, and then repeated for the fellow eye
Tea Tree Oil

- Tea tree oil, or melaleuca oil
- Taken from the leaves of the Melaleuca alternifolia
- Is native to Southeast Queensland and the Northeast coast of New South Wales, Australia
- Toxic when taken by mouth, but is widely used in low concentrations in cosmetics and skin washes
Lipid Based Products
Lipiflow
• 3x gland improvement
• 2x symptom improvement
• Improvement seen beyond 9-months
• Safe
• Well Researched
Alcon
iLux Device
Alcon
iLux Device
Sight Sciences
Tear Care System
Sight Sciences - Tear Care System
Traditional Thoughts – Treat Topically
Why Do Omega 3’s Work?

Eicosapentaenoic acid / Docosahexaenoic acid (EPA/DHA)

Cyclooxygenase

Prostaglandin - 3 (Anti-inflammatory)
IMPORTANT:

Fish Oil ≠ EPA/DHA

>70%
Cyclosporine Ophthalmic Emulsion 0.05%

- Manufacturer: Allergan, inc

- Active Ingredients: Cyclosporine 0.05%

- Inactive Ingredients: Glycerin, Castor Oil, Polysorbate 80, Carbomer 1342, and purified water

- Preservation: None (unit-dose vile)
Cequa™
(cyclosporine ophthalmic solution) 0.09%

60 SINGLE-USE VIALS
6 pouches x 10 single-use vials (0.25 mL each)

Rx only
Keep out of reach of children.
Not child resistant.

For topical use in the eye
Sterile, Preservative-Free

NDC 47355-506-06

SUN PHARMA
What if they have rosacea?
Meibomian Gland Dysfunction Treatment

- Oral Antibiotics
- Doxycycline
  - 20 to 200 mg bid po x 1-2 months, then taper
The effect of low-dose doxycycline therapy in chronic meibomian gland dysfunction

Yoo SE1, Lee DC Chang MH.

- Patients with meibomian gland dysfunction unresponsive to eyelid hygiene
- 150 patients randomized to 20 mg bid p.o. or 200 mg bid p.o.
- Identical effectiveness
- 39% of high dose experienced side effects vs. 17% of low dose
Meibomian Gland Dysfunction Treatment

- Oral Antibiotics
- Side Effects
  - Gastrointestinal upset
  - Yeast infections
  - Photosensitivity
  - Do not prescribe to children and pregnant women
  - Shouldn’t be taken with milk or dairy products
Doxycycline hyclate 100mg bid p.o. vs. topical Azithromycin 1% bid for 2 days then qd for 2 months
Punctal Occlusion
Signal Strength

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Jewelers Forceps
Punctal Plugs

Permanent

- Pedi-Plug
- X-Small
- Small
- Medium
- Large
- X-Large

Temporary

Collagen (10-14 days)
- 0.2 mm
- 0.3 mm
- 0.4 mm

3 month
- 0.2 mm
- 0.3 mm
- 0.4 mm
- 0.5 mm

6 month
- 0.3 mm
- 0.4 mm
- 0.5 mm

Recently Became Available
Various Size Puncta

0.2 mm 3 month

0.4 mm collagen
Before Plugs

2 weeks
The Amniotic Membrane

- The amniotic membrane is the innermost lining of the placenta (amnion)
- Amniotic membrane shares the same cell origin as the fetus
  - Stem cell behavior
- Structural similarity to all human tissue
The Fitting Philosophy

- Limbal Clearance
- Central Corneal Clearance
- Scleral Landing
Provide Relief
+
Improve function
Provide Relief?

Lipid Based

Ointment

Aqueous Based

Gels
Mechanical

1. MG Function
2. Retain Tears
3. Clean lids
Determine the Cause

Set Appropriate Treatment Plan

1. Provide Relief

2. Improve Function

Mechanical

Chemical
Dry Eye Work-up / Follow-up

1) History
   a. Ocular Surface Disease Index
   b. SPEED Questionnaire

2) Tear film breakup time
   a. Less than 10 seconds is low

3) Tear film breakup pattern

4) Corneal staining - fluorescein

5) Conjunctival staining - fluorescein

6) Corneal staining – Lissamine green/rose bengal

7) Conjunctival staining - Lissamine green/rose bengal

8) Lid Wiper epitheliopathy

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9) Lid laxity/elasticity

10) Lid margin assessment
   a. Hyperemia; presence of debris at base of lashes
   b. Irregularity that is present at the margin
   c. Line of Marx

11) Quality of meibum expressed from glands
   a. Meibomian gland evaluator

12) Structure of Meibomian glands (eyelid transillumination); infrared imaging

13) InflammaDry (strong positive, weak positive, negative)

14) Phenol red thread test
   a. Thread is left in place for 15 seconds
   b. Less than 10mm suggests a tear deficiency
Artificial tears
Type: Systane Complete / Systane Balance / Refresh Optive Advanced / Fresh Kote
Other: ______________________
Directions: 1-2 drops, ___ times per day

Thermal therapy
Bruder Heat mask
Other: ______________________

Ocular nutrition
EZ Tears – 2 capsules once per day before meal
Other: ______________________

Topical antibiotics
Azasite, Erythromycin
Other: ______________________
Directions: ____________________

Restasis / Xiidra
Directions: 1 drop twice a day
Other: ______________________

Steroids
Lotemax / FML / Flarex
Other: ______________________
Directions: ____________________

Doxycycline
Directions: ____________________

3% testosterone cream
Directions: ____________________

Other: ______________________
Thank You
mile.bruijc75@gmail.com