Systemic Inflammation and Ocular Surface Disease

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objectives

Detail OSD testing suggestive of systemic inflammation

Identify key co-management goals

Describe advanced OSD treatments to improve QOL

Epidemiology of OSD

The Dry Eye Stats

35% of the population with at least with some symptoms
- 2/3 women

2017 study: ~7% for a total of some 16.8 million diagnosed

Economic burden
- US 2011: $55 billion
- US 2019: $600 for mild dry eyes to over $3000 for severe dry eye per patient per year

Common
- 20% of visits are for dry eye complaints

Aqueous deficiency

Sjogren's vs. Non-Sjogren's

Primary Sjogren's
- Anti SSA (Rho) and Anti SSB (La)

Secondary Sjogren's
- Other inflammatory causes
  - Egs. RA, SLE, Scleroderma, Hashimotos, Hepatitis

Non – Sjogren's
- Primary lacrimal deficiency
  - Aging, AIDS, dysautonomia, GVHD, nerve ablation
- Lacrimal duct obstruction
- Reflex hyposecretion
  - DM, CL wear, neurotrophic

Latest international classification

1. Antibodies
2. Lip biopsy showing a high density of infiltrated cells
3. Low Schirmer's less than 5mm in 5 minutes. NO anesthesia
4. Low salivary production

The dry eye and dry mouth and either AB or Biopsy positivity are sufficient for diagnosis.

Recall 1 in 7 may develop NHL

Conjunctival staining

Intrapalpebral staining is indicative of aqueous deficiency

KCS
Keratoconjunctivitis Sicca

Itis = inflammation

Sicca = dryness

KCS is chronic and progressive

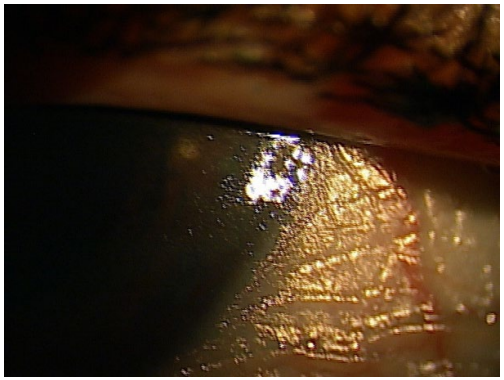
Treatment

- Improve S/S
- Sometimes stability is a win

Evaporative

Types

INTRINSIC	EXTRINSIC
MGD	Vitamin A
Lid issues	CL wear
Blink	Topical meds
Systemic med	Allergic eye disease



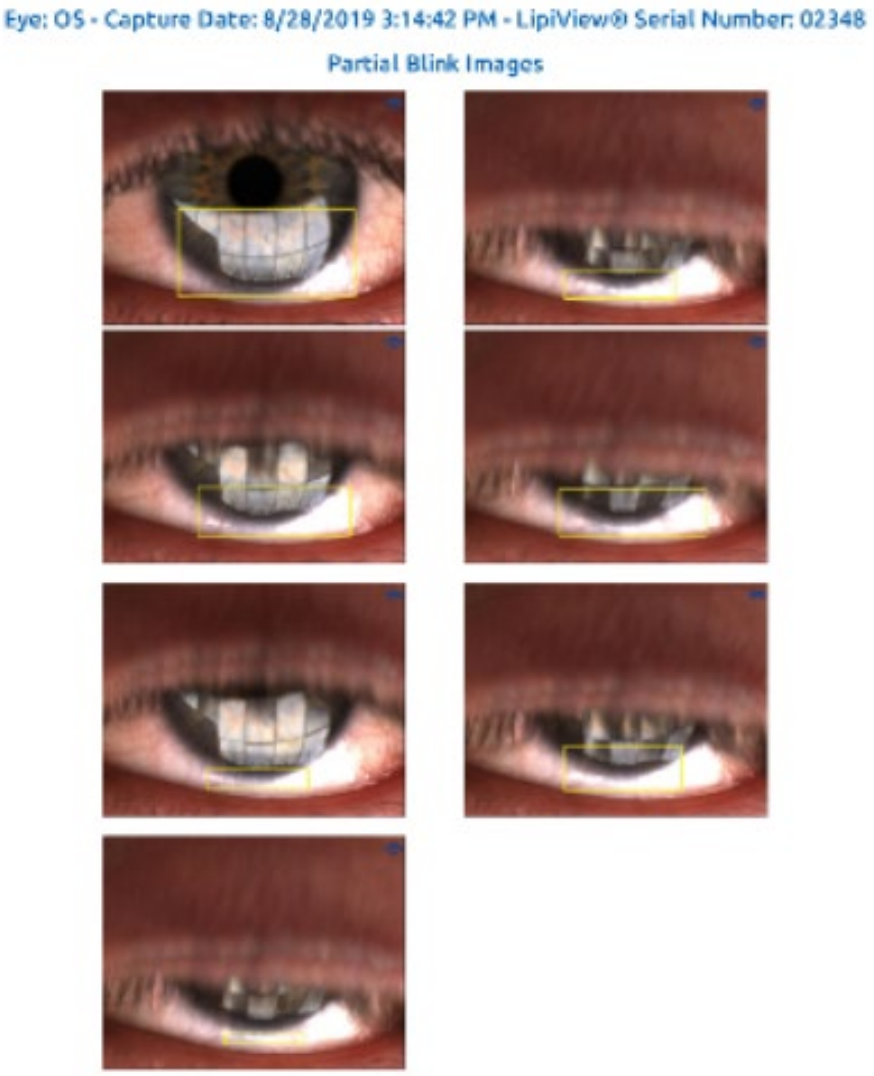
Growing impact of digital devices on dryness

Impact on the blink
- Reduced frequency
- Partial blinks

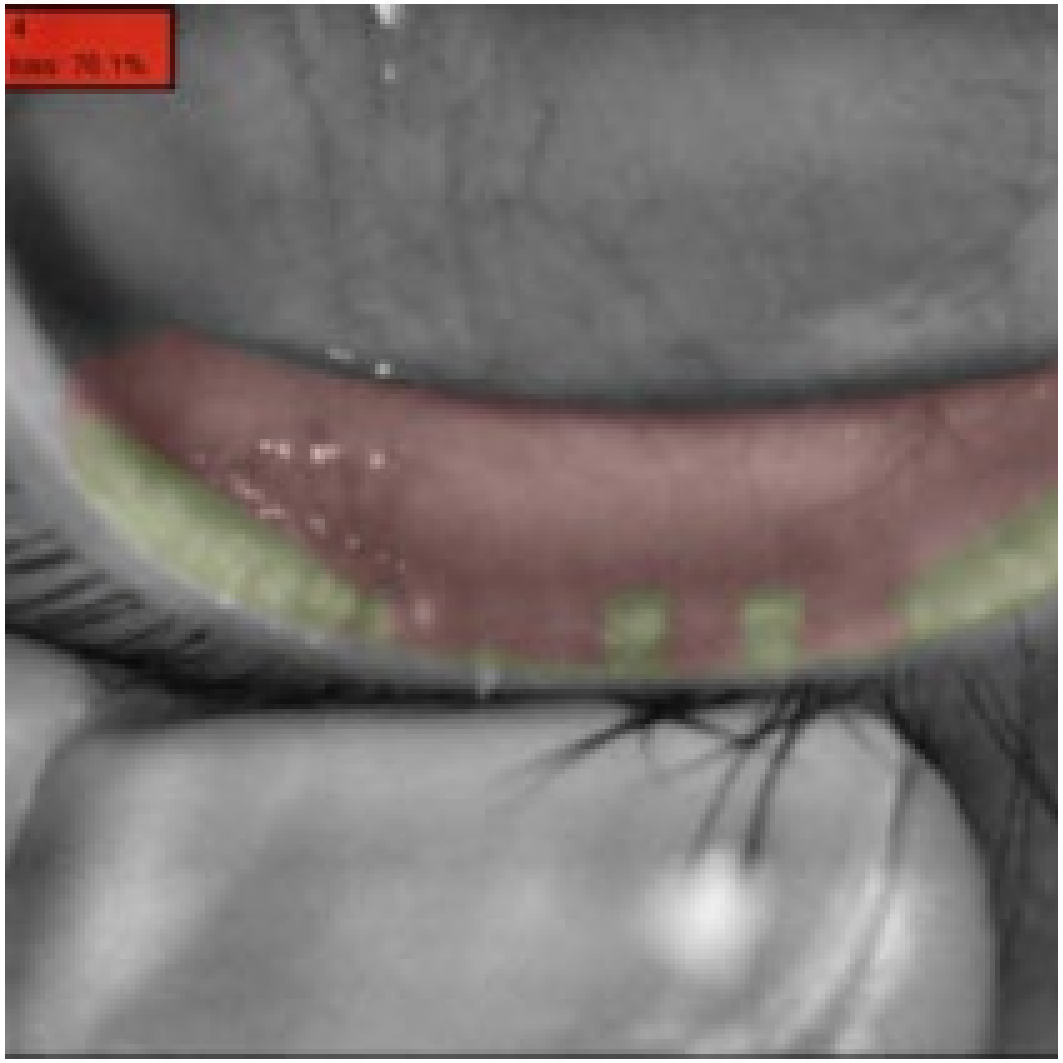
Impaired meibomian function

Decreased lipid layer

Impaired blinking



Severe loss due to use of isoretinoin



Mucin disruption

Mucin disruption

Increased in allergy

Allergic rhinoconjunctivitis increasing

Bloodwork vs. testing

The work up

The workup

1. History: validated questionnaire
2. Osmolarity: the concentration of the tears
   Over 308 or more then 10 difference between eyes abnormal and suggests additional tests
3. MMP9: tear sample to test for inflammation
   ANY pink is abnormal
4. Imaging/Meibography
   Glands, tear meniscus, NIBUT, redness

Ocular Surface Disease Index® (OSDI®)[2]

Ask your patient the following 12 questions, and circle the number in the box that best represents each answer. Then, fill in boxes A, B, C, D, and E according to the instructions beside each.

HAVE YOU EXPERIENCED ANY OF THE FOLLOWING *DURING THE LAST WEEK*:

	All of the time	Most of the time	Half of the time	Some of the time	None of the time
1. Eyes that are sensitive to light?	4	3	2	1	0
2. Eyes that feel gritty?	4	3	2	1	0
3. Painful or sore eyes?	4	3	2	1	0
4. Blurred vision?	4	3	2	1	0
5. Poor vision?	4	3	2	1	0

Subtotal score for answers 1 to 5 (A)

HAVE PROBLEMS WITH YOUR EYES LIMITED YOU IN PERFORMING ANY OF THE FOLLOWING *DURING THE LAST WEEK*:

	All of the time	Most of the time	Half of the time	Some of the time	None of the time	
6. Reading?	4	3	2	1	0	N/A
7. Driving at night?	4	3	2	1	0	N/A
8. Working with a computer or bank machine (ATM)?	4	3	2	1	0	N/A
9. Watching TV?	4	3	2	1	0	N/A

Subtotal score for answers 6 to 9 (B)

HAVE YOUR EYES FELT UNCOMFORTABLE IN ANY OF THE FOLLOWING SITUATIONS *DURING THE LAST WEEK*:

	All of the time	Most of the time	Half of the time	Some of the time	None of the time	
10. Windy conditions?	4	3	2	1	0	N/A
11. Places or areas with low humidity (very dry)?	4	3	2	1	0	N/A
12. Areas that are air conditioned?	4	3	2	1	0	N/A

Subtotal score for answers 10 to 12 (C)

ADD SUBTOTALS A, B, AND C TO OBTAIN D (D = SUM OF SCORES FOR ALL QUESTIONS ANSWERED) (D)

TOTAL NUMBER OF QUESTIONS ANSWERED (DO NOT INCLUDE QUESTIONS ANSWERED N/A) (E)

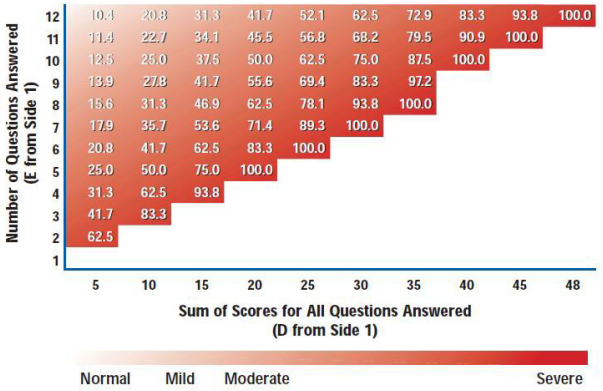
Please turn over the questionnaire to calculate the patient's final OSDI® score.

Evaluating the OSDI® Score[1]

The OSDI® is assessed on a scale of 0 to 100, with higher scores representing greater disability. The index demonstrates sensitivity and specificity in distinguishing between normal subjects and patients with dry eye disease. The OSDI® is a valid and reliable instrument for measuring dry eye disease severity (normal, mild to moderate, and severe) and effect on vision-related function.

Assessing Your Patient's Dry Eye Disease[1,2]

Use your answers D and E from Side 1 to compare the sum of scores for all questions answered (D) and the number of questions answered (E) with the chart below.*
Find where your patient's score would fall. Match the corresponding shade of red to the key below to determine whether your patient's score indicates normal, mild, moderate, or severe dry eye disease.



*Values to determine dry eye disease severity calculated using the OSDI® formula:
$\text{OSDI}^{®} = \frac{(\text{sum of scores}) \times 25}{(\#\text{ of questions answered})}$

Patient's Name: _____ **Date:** _____

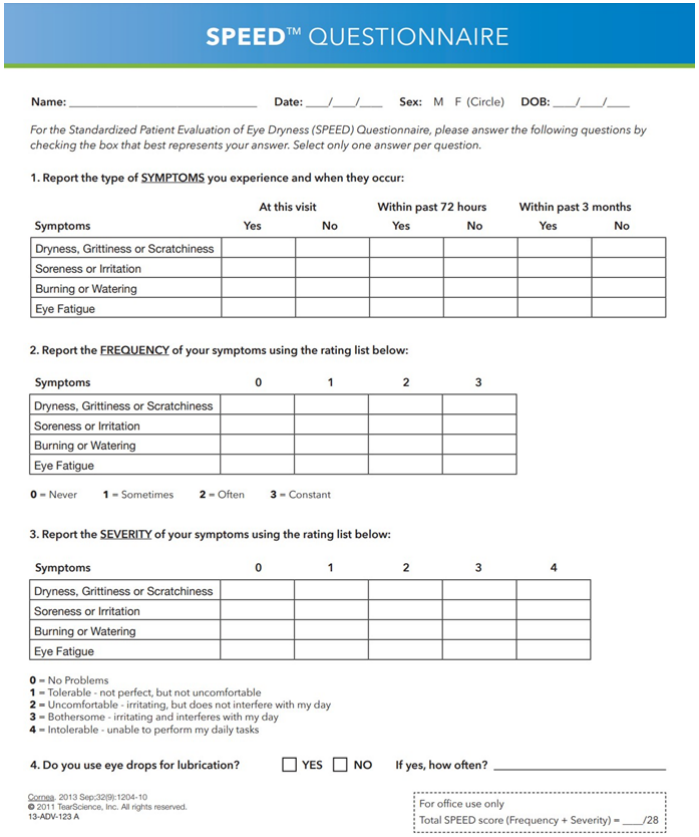
How long has the patient experienced dry eye? _____

Eye Care Professional's Comments: _____

Tear and place in patient's chart for follow-up care on next visit.

This is what we use in KYCO's Advance Cornea Care Service

SPEED QUESTIONNAIRE



SPEED™ QUESTIONNAIRE

Name: _____ **Date:** ___/___/___ **Sex:** M F (Circle) **DOB:** ___/___/___

For the Standardized Patient Evaluation of Eye Dryness (SPEED) Questionnaire, please answer the following questions by checking the box that best represents your answer. Select only one answer per question.

1. Report the type of SYMPTOMS you experience and when they occur:

Symptoms	At this visit		Within past 72 hours		Within past 3 months	
	Yes	No	Yes	No	Yes	No
Dryness, Grittiness or Scratchiness						
Soreness or Irritation						
Burning or Watering						
Eye Fatigue						

2. Report the FREQUENCY of your symptoms using the rating list below:

Symptoms	0	1	2	3
Dryness, Grittiness or Scratchiness				
Soreness or Irritation				
Burning or Watering				
Eye Fatigue				

0 = Never **1** = Sometimes **2** = Often **3** = Constant

3. Report the SEVERITY of your symptoms using the rating list below:

Symptoms	0	1	2	3	4
Dryness, Grittiness or Scratchiness					
Soreness or Irritation					
Burning or Watering					
Eye Fatigue					

0 = No Problems
1 = Tolerable - not perfect, but not uncomfortable
2 = Uncomfortable - irritating, but does not interfere with my day
3 = Bothersome - irritating and interferes with my day
4 = Intolerable - unable to perform my daily tasks

4. Do you use eye drops for lubrication? ☐ YES ☐ NO **If yes, how often?** _____

Cornea. 2013 Sep;32(9):1204-10
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13-ADV-123 A

For office use only
Total SPEED score (Frequency + Severity) = ___/28

Standard Patient Evaluation of Eye Dryness (SPEED)

Quicker
Gaining popularity

Severity

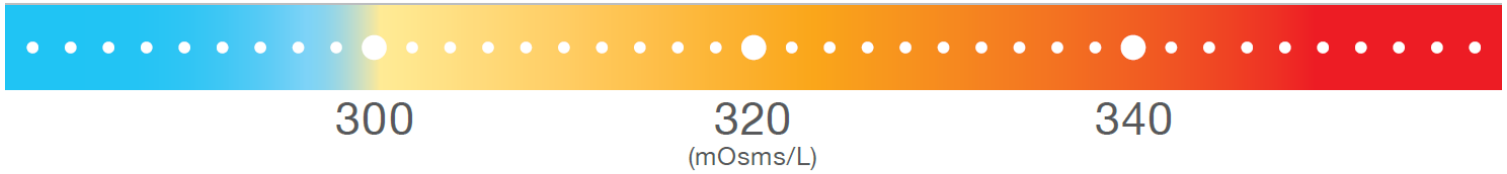
- 0-4 Mild
- 5-7 Moderate
- 8+ Severe

Tear Lab- osmolarity

Osmolarity Measurements

Right Eye (OD) _____ (mOsms/L) Left Eye (OS) _____ (mOsms/L)

Inter-eye difference is > 8mOsm/L	☐ Yes	☐ No	
Osmolarity	☐ Normal	☐ Abnormal	
Patient Dry Eye Severity	☐ Mild	☐ Moderate	☐ Severe
Schedule for Dry Eye Workup	☐ Yes	☐ No	



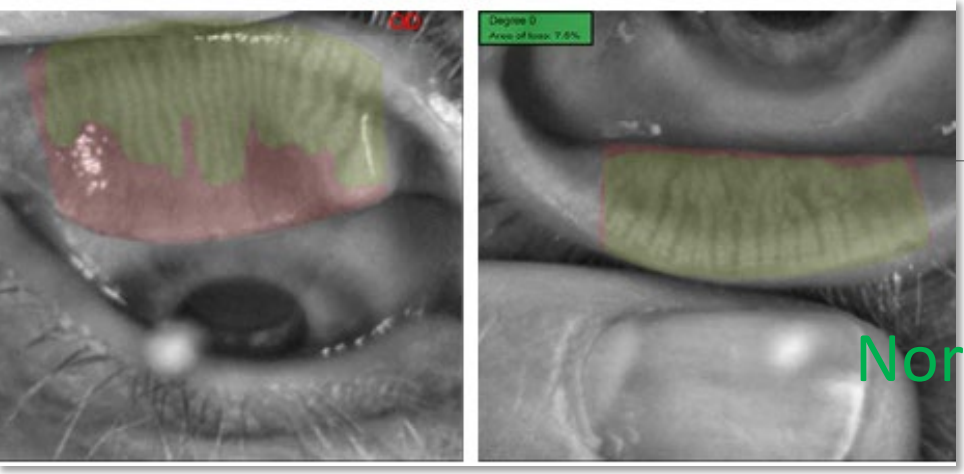
Weak and strong positive MMP9 results

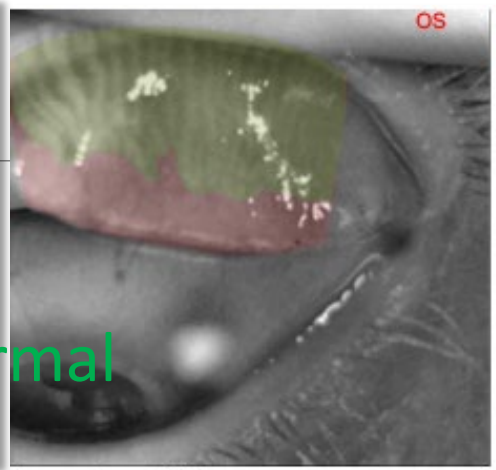
Based on the results of a 300 patient trial that was presented at the 2009 American Academy of Ophthalmology, osmolarity correctly identified

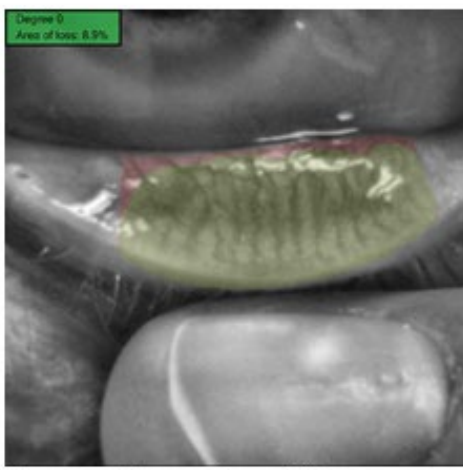
- 88% of normal subjects
- 75% of mild/moderate disease subjects
- 95% of severe disease subjects
- diagnostic cut-off of 308 mOsms/L.[1] Therefore, osmolarity values above 308 mOsms/L are generally indicative of dry eye disease.

[1] Foulks GN, Lemp MA, Berg M, Bhola R, Sullivan BD. TearLab™ Osmolarity as a Biomarker for disease severity in mild to moderate dry eye disease. American Academy of Ophthalmology PO382, 2009

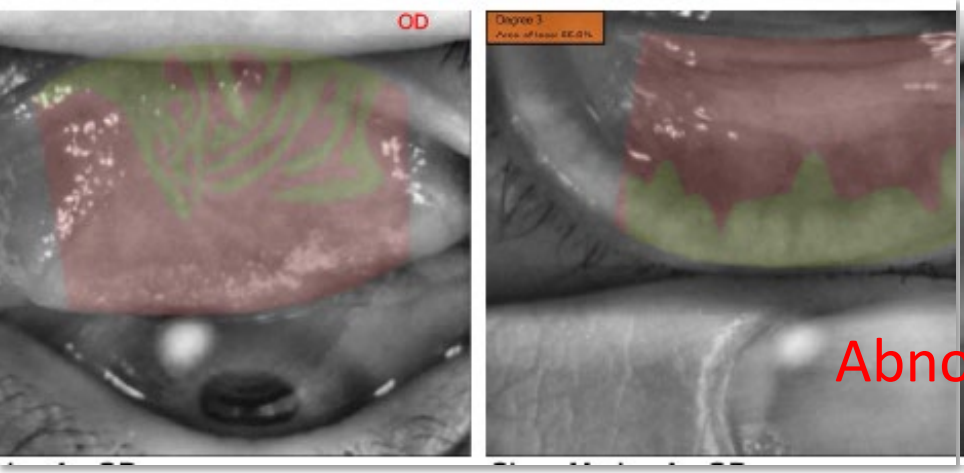
[2] Sullivan BD et al., "Diagnostic performance of osmolarity combined with subset markers of dry eye disease in an unstratified patient population". ARVO 2010.

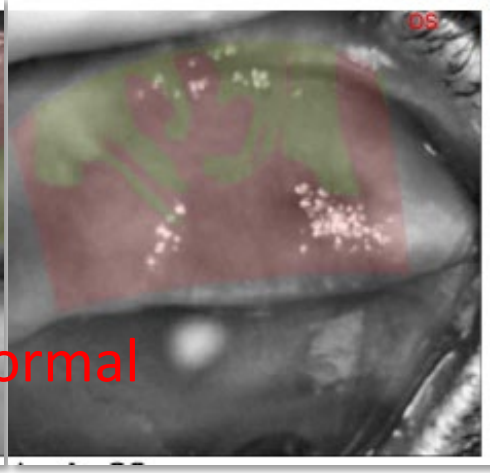


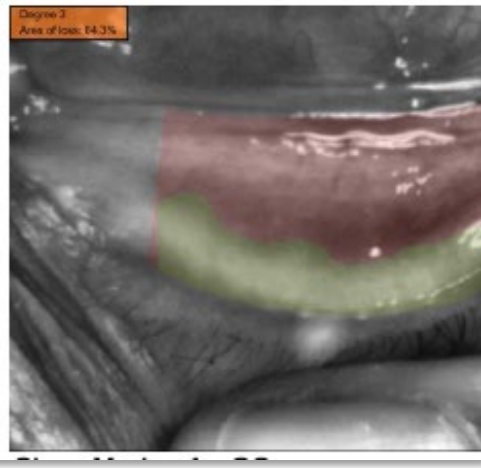




Normal







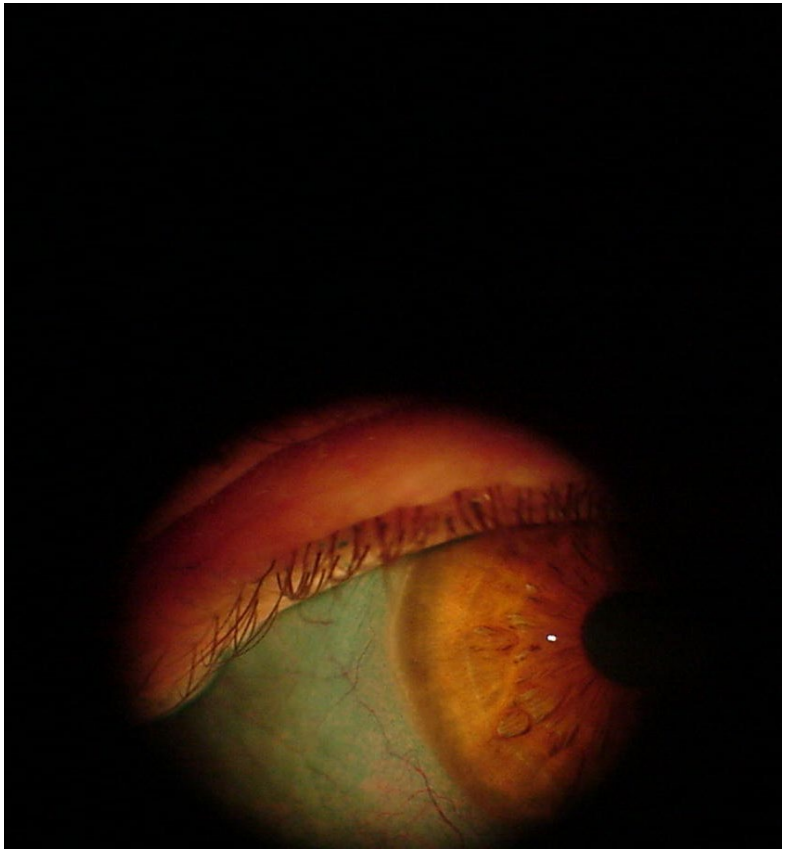
Abnormal

Structure

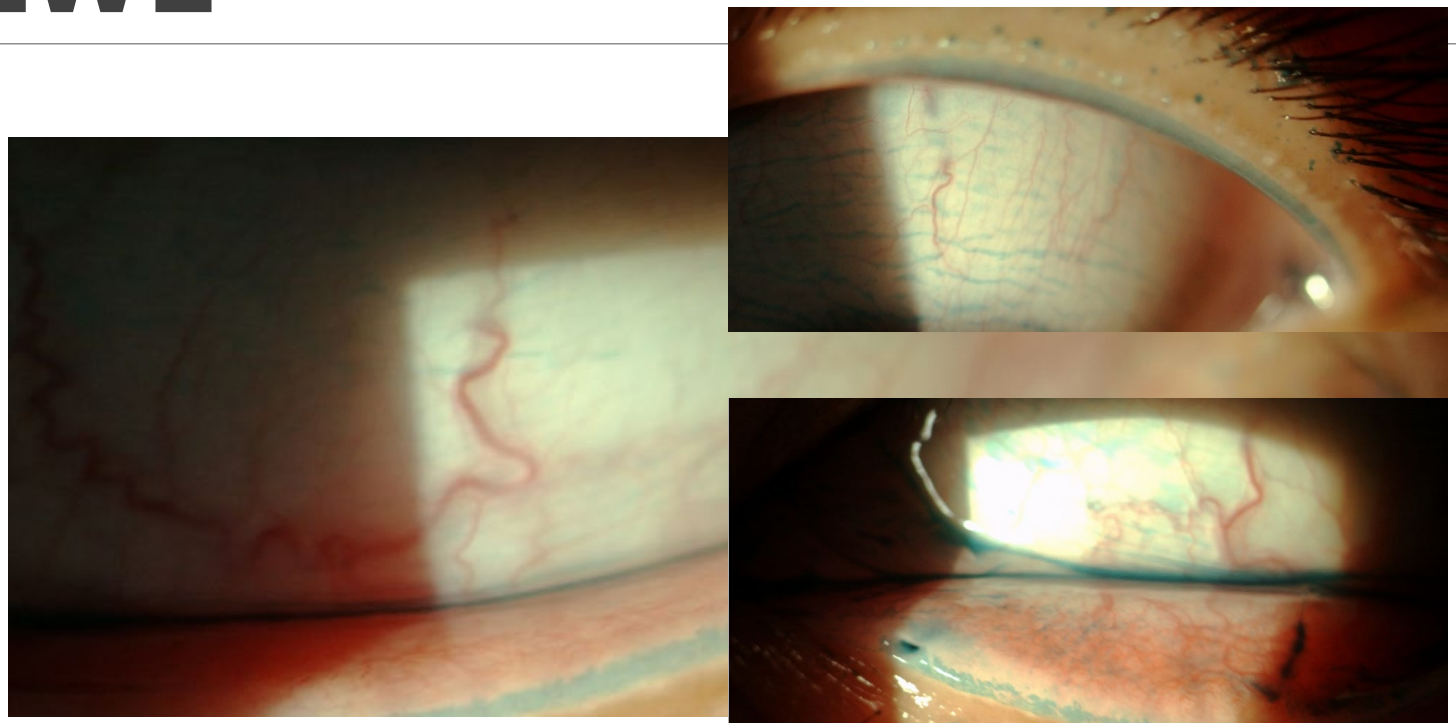
5. Slit lamp
   - Redness
   - Lid margin
   - Cornea
6. Schirmer I https://vimeo.com/198695983
   - No anesthetic
   - Less than or equal to 5mm in 5 min highly suggestive of Sjogrens or other systemic/ autoimmune mediated dry eye
   - Closed eyes
   - Unlike the video the strips should be temporal so there is minimal irritation to the cornea

7. Stains and more invasive slit lamp evals
    1. Instill LG and NaFL simultaneously
        1. Assess LG first it stains dead and devitalized cells and will show up right away. You do need a good volume of stain.
        2. Then assess NaFL and TBUT: 15 sec to fluoresce
    - Assess MG function with digital pressure or MGE
    - Evert lids and look for papillae
    - Swirl lashes for demodex

Conjunctival Stain with Lissamine Green



LWE



Conjunctival staining

Intrapalpebral staining is indicative of aqueous deficiency

Gland Evaluation

Changes to the meibomian gland secretions
- Turbidity → increased viscosity → pasty

Presence of pouted, capped or pointed glands

Frothing (saponification)

https://www.youtube.com/watch?v=KKrymT5R2Hk

Gland function

Changes to the meibomian gland secretions
- Turbidity → increased viscosity → pasty

Presence of pouted, capped or pointed glands

Frothing (saponification)

Meibomian gland evaluation (MGE)
- Attempts to normalize the pressure applied to the lid
- Small tool expresses evenly 5 or so glands at at time

8. Bloodwork
   - Based on complaints (dry mouth, joint pain, tooth loss) consider ordering bloodwork
   - SJO test or individual tests
     - ESR, ANA, RF, SSA, SSB
   - Chem panel
     - Hep C/Hep B
   - If positive refer to rheumatology

9. Neuropathic component
   - Corneal sensitivity
   - Cochet bonet testing

8. Bloodwork
   - Either order yourself or send request to PCP
   - Based on complaints (dry mouth, joint pain, tooth loss) consider ordering bloodwork
   - Looking for autoimmune disease
     - ESR, CRP, ANA, RF, SSA, SSB
     - SJO test
   - If positive, refer to rheumatology for evaluation

Sjo test- proprietary

Looks specifically for sjogrens and is owned by Immco labs

ANA= anti-nuclear antibodies

RF= rheumatoid factor

SSA= sjogrens A/Ro

SSB= sjogrens B/La

Adds unique markers

SP1= salivary protein 1

CA6= carbonic anhydrase 6

PSP= parotid secretory protein

My favorite

labcorp

Use a keyword, test name or number

ANA 12 Plus Profile, Do All (RDL)

TEST: 520175

CPT: 86038; 86147(x3); 86160(x2); 86200; 86225; 86235(x6); 86256; 86376; 86431

Synonyms	• ANA 12 Plus • ANA 12 Plus Panel
Test Includes	This profile is comprised of Anti-Nuclear Ab (ANA) by IFA, Anti-dsDNA Ab by Farr, Anti-ENA Abs (Anti-Sm & Anti-RNP), Anti-Centromere Ab, C3 & C4 Complements, Anti-Ro (SS-A) Ab, Anti-La (SS-B) Ab, Anti-Scl-70 Ab, Anti-cardiolipin Abs (IgG, IgA & IgM isotypes), Anti-TPO (Thyroid Microsomal Peroxidase) Ab, Anti-Chromatin Ab, Rheumatoid Factor by Turb, Anti-CCP (Cyclic Citrullinated Peptide) Ab. The reflexive ANA 12 Plus Profile is a separate test (use 520180).

Associated conditions

Systemic sclerosis

Localized (skin signs only) and systemic types

Often overlaps with other autoimmune disease
- Referred to as overlap syndrome (20%)

Ocular signs
- Severe ADDE
- Increased risk of lid disease due to changes to skin
- Poor retinal perfusion

Lupus

Ocular signs in 50%

ADDE

Uveitis

Scleritis

PUK

Choroidopathy

Retinopathy

Periphlebitis

Nerve palsies

Sjogrens

Dry everything

Tooth loss and tooth decay

Arthritis

Vasculitis

Kidney disease

Cardiac disease

Myocarditis

Ocular: ADDE, Intermediate uveitis

RA

Ocular

- PUK
- Moorens
- Scleritis
- ADDE
- Uveitis

Ankylosing Spondylitis

1 in 4 experience acute anterior uveitis

25% of males with acute anterior uveitis cases are also have ankylosing spondylitis

Episcleritis

Scleritis

ADDE/Secondary Sjogrens

Reactive arthritis (formerly Reiter's syndrome)

Ocular S/S

- Conjunctivitis (Common)
- AAU (20%)
- Episcleritis

Psoriatic arthritis

Eye S/S

- Anterior uveitis (7-20%)
  - Bilateral
  - Chronic
  - Severe
- Conjunctivitis
- ADDE/Sjogrens

Ulcerative colitis

Ocular S/S

- Uveitis 5%
- Episcleritis
- Scleritis
- Conjunctivitis

Chron disease

Ocular inflammation in ~12%

- Anterior uveitis 3%
- Episcleritis
- Scleritis
- Conjunctivitis
- Myositis
- Optic neuritis

Sarcoid ocular signs

Uveitis

- Mutton fat KP
- PAS
- Snowballs
- Chorioretinal lesions
- Periphlebitis

Granulomatous nodules may appear in many ocular tissues

Celiac

May have Sjogren's as an overlap disease

Vitamin A deficiency may result in severe dry eye

Celiac patients have lower Schirmer's and lower TBUTs than control patients

Uzel, M., Citirik, M., Kekilli, M. *et al.* Local ocular surface parameters in patients with systemic celiac disease. *Eye* **31**, 1093–1098 (2017). https://doi.org/10.1038/eye.2017.31

Infectious suspect additions

CBC with chem panel
- Looking for liver enzymes

Titres
- HCV
- HBV
- HSV
- VZV

Syphilis serology

PPD

Associate derm condition

Acne Rosacea

May overlap with autoimmune disease

Can mimic ocular cicatricial pemphigoid

Demodecosis association

Increased inflammation

Severe lipid deficiency dry eye

In conjunction with autoimmune disease will lead to mixed mechanism to dryness

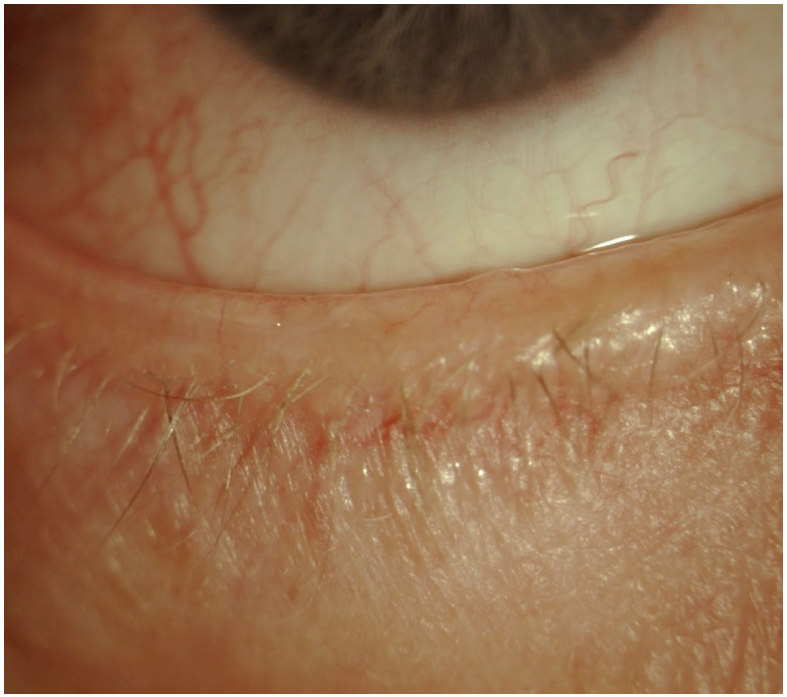
Ocular rosacea

May exist without other facial signs and may include

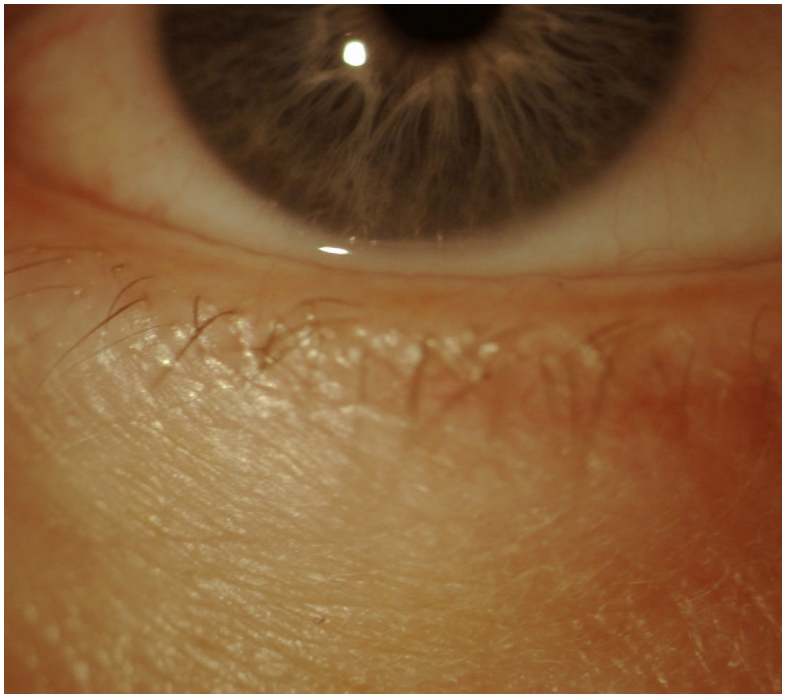
- Blepharitis
- Inflammation
- Tearing
- Chalazia
- Hordeola
- Corneal vascularization
- Corneal and/or conjunctival scarring
- Corneal thinning
- Perforation

Telangiectasia

BEFORE METROGEL



AFTER METROGEL



In office dry eye treatments

Options

Biofilm removal
- Tea tree
- Okra
- Hypochlorous
- Forceps

Lid exfoliation

Lid debridement

Expression

Plugs (only one with a billing code)

Meibomian gland probing

Seldom used as it is painful

Maskin probe or a needle is inserted into the MG opening to remove the “clog”

Expression/Evacuation

Manual
- Warm the lids
- Masks
- Blephasteam
- MiBo thermaflow
- Tearcare
- RF

Mechanical
- iLux
- Lipiflow

Advanced strategies

IPL

Intense pulsed light therapy (IPL)

Reduces inflammation

Used in rosacea treatment
- With eyeshield in place

Most treatments are performed along the zygomatic arch and across the nose

Increasing use on lids
- Documented sequelae with old instruments include
  - Severe uveitis
  - Iris transillumination defects
  - Changes in lid pigment
- Newer instruments appear to be safer and may be used with a barrier to minimize impact to the uvea

Marked improvement in telangiectasia

Improvements in collagen formation

More fluid meibum
- May be done in conjunction with expression as it does heat the lid

Approvals

Rosacea FDA
- Lumenis M22
  - Recommend treatment tragus to tragus (Toyos settings)
  - Facial treatmetns to reduce telangiectasia and blend in any bleaching associated with vascular Toyos settings.
  - Requires cooling tip and cooling gel
- Eye-light 5 treatments per side
  - 4 vertical and one horizontal

Ophthalmic FDA
- Optilight by Lumenis
- Expands skin types you can treat and adds a small wand for better control of lid treatments

IPL studies show improved

OSDI and SPEED dry eye survey scores

Appearance of lid margin

Vision

Meibography

Staining

Schirmer

Telangectasia

Lipid tear film analysis

Osmolarity

Quality of meibum

Treatment strategies

3-4 IPL treatments 3-4 weeks apart

Lid debridement

- Remove clogs and debirs

Meibomian gland evacuation

- Mechanical heating of lids with use of hydraulic or compressive techniques to express all unhealthy meibum
- Reset the system

Maintenance required

Punctal occlusion with silicone plugs

RISKS

Infection

Stagnation

Inflammation

Pyogenic granuloma

BENEFITS

Patient's own tears

Increases tear volume

Certain types can be removed

May help determine who would be a good candidate for cautery

Preferred after inflammation is controlled.

Therapeutic options

Sclerals

- Moisture reservoir
- Lens fluid considerations
  - Buffered vs. non buffered
  - Supplementation
- If have systemic severe dry eye related diagnosis may be covered under medical (v2627)
  - PROSE- prosthetic replace of the ocular surface ecosystem

Bandage lenses

May be used for patients struggling with various ocular surface diseases including

- Bullous keratopathy
- Recurrent erosions
- Abrasions
- Trichiasis

Antibiotic prophylaxis

- EW lenses increase of risk infection
- Therefore, it is common practice to prescribe an antibiotic to use with the BCL

Therapeutic approvals

Today's lenses

- Oasys, N&D, Purevision
- All have overnight approval as well.
- Thus, can be used for extended use.

In more chronic conditions Purevision and N&D can be used on-label for up to 30 days

Oasys is only approved for 6 days of EW

Protocols

- Consent due to increased risk of infection
- Apply lens
- Instill antibiotic
- 1 day follow up
  - Telehealth vs. in person
- Patient to use prophylactic antibiotic and tears
  - No ointments
- Based on healing next visit may vary
  - 1 week
  - 3 week
- Removal
  - Float the lens
    - Irrigate profusely
  - Remove using slit lamp and forceps
    - Gently slide the forceps under the inferior edge of the lens

Biologic

AMNION AND BLOOD DERIVED PRODUCTS

Regener-Eyes

Placenta derived growth factors and anti-inflammatory cytokines

"ground up amnion"

Two strengths

Lite

- Temperature stable
- Once a day dosing

Professional

- Must be refrigerated
- QID dosing

Blood derived products

Serum tears

Autologus= from the patient's own blood

Blood is drawn

Spun down

Diluted to designated concentration
- 20-50%

Individual vials

Keep chilled

Dosed as often as q2h

Platelet Rich Plasma Tears

Similar to serum tears however platelets are added back in

May provide added healing for some patients

Albumin drops

Not autologous

Purchased from compounding pharmacy

Serum albumin is commercially available

Amniotic membranes

Cryopreserved approved for wound healing

Placed for 3-7 days

Improved healing and often decreased sensitivity for patients with neuropathic component

Dehydrated: approved for wound covering, less evidence on healing and use in dry eye

cases

41 yowf

Domestic violence survrivor in recovery

Seasonal and periennial allergies

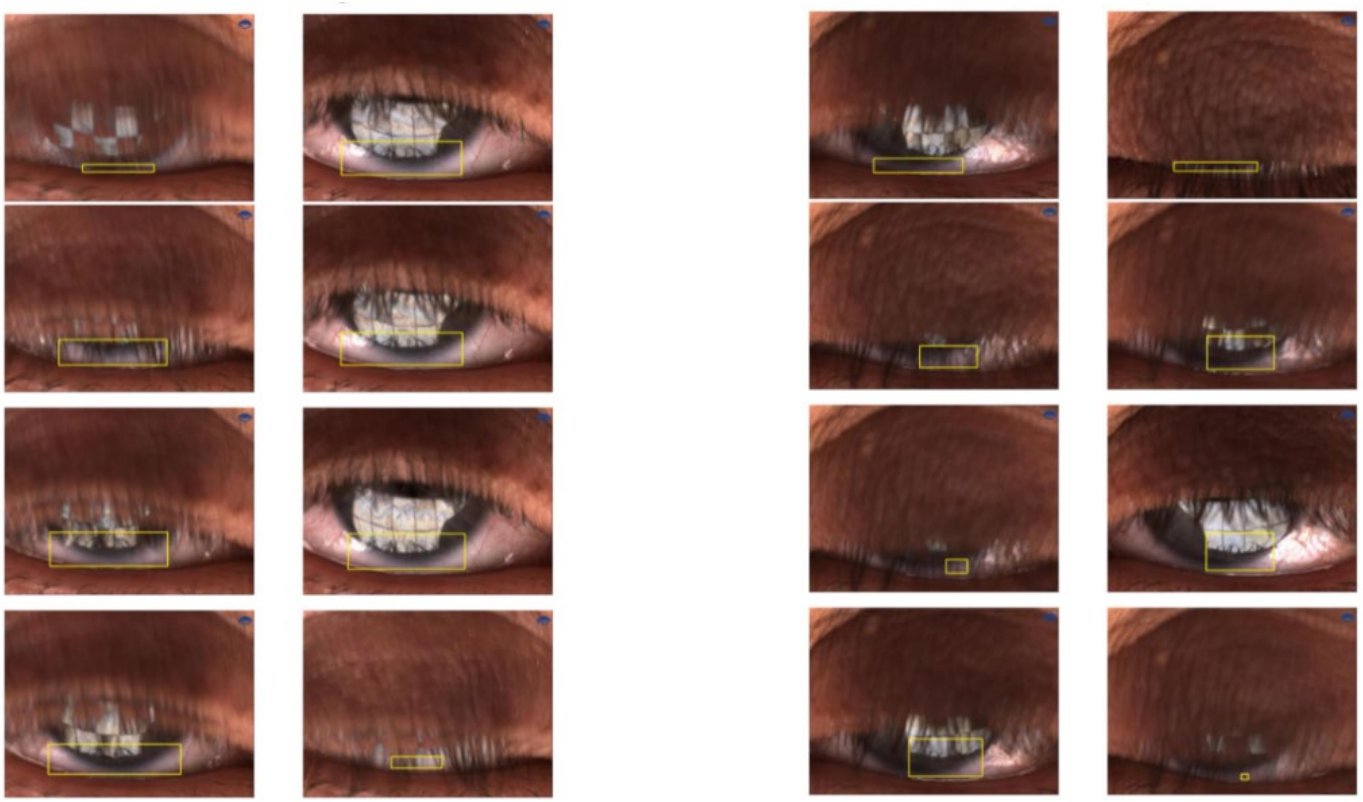
CC: severe dryness and ocular itching associated fatigue

Meds: suboxone, Claritin, flonase

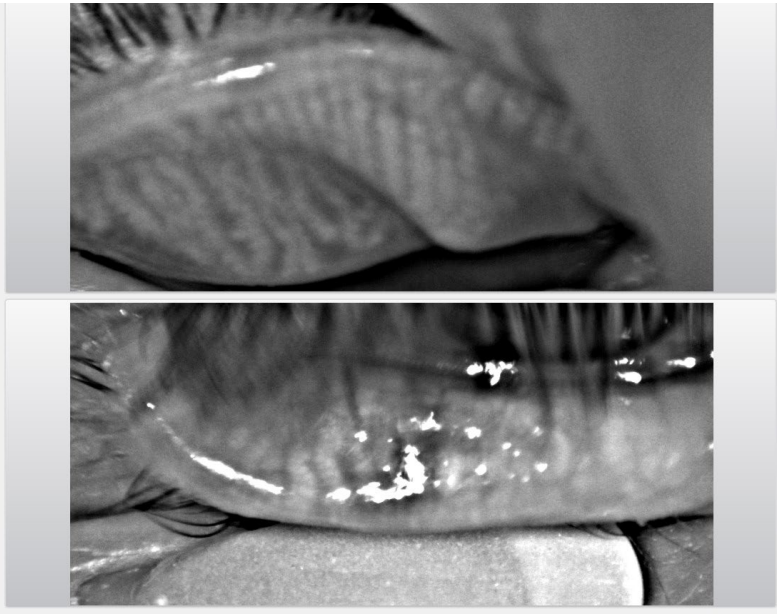
Baseline testing

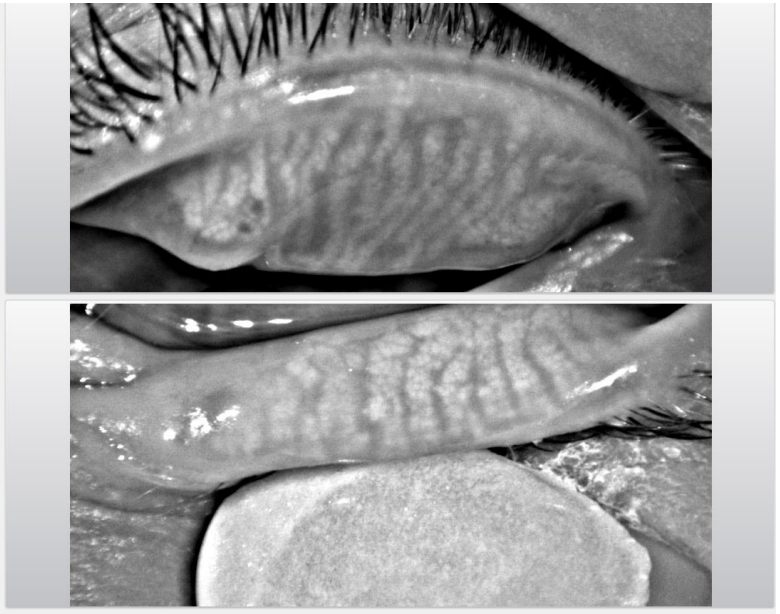
OSDI:	75 = Severe
Osmolarity:	297 OD 335 OS
Inflammadry:	Strong positive OU
Schirmer:	11mm OD 14mm OS

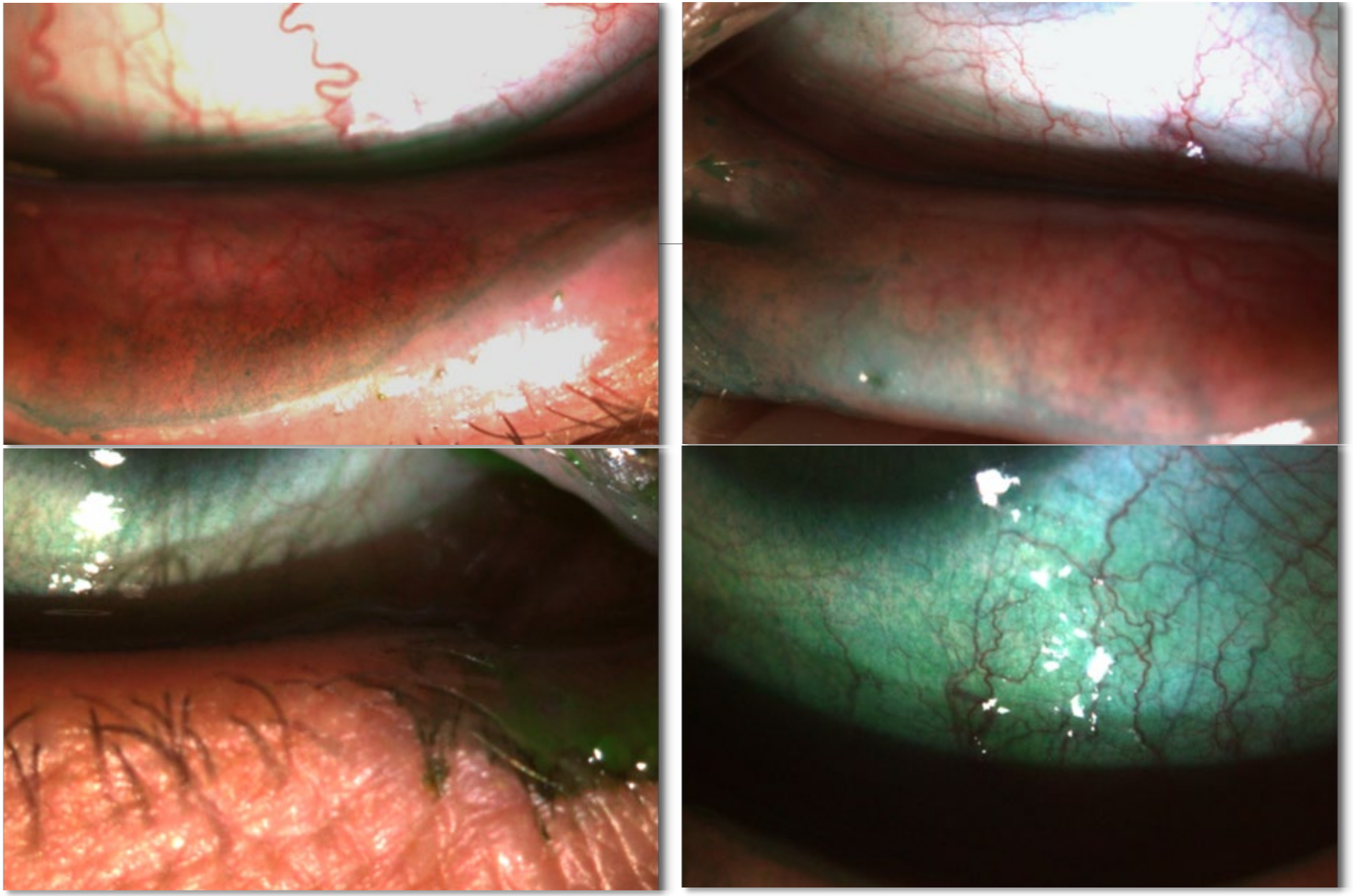
Poor blinks



Damaged meibomian glands







Consult with PCP

Requested autoimmune testing at next visit

They also ran standard CMP and CBC with diff

Liver enzymes severely elevated

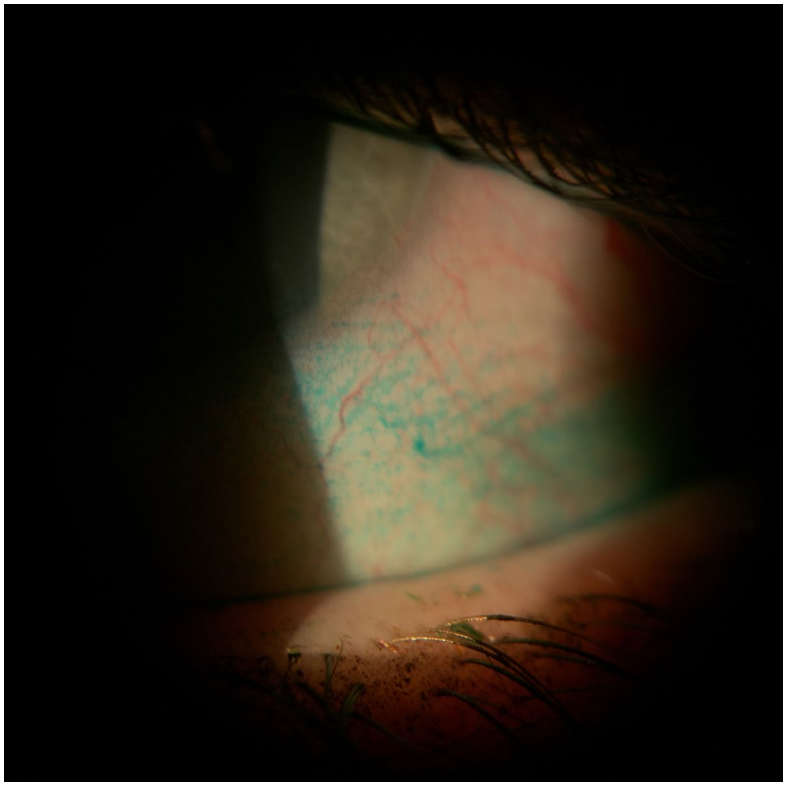
Subsequently Hep testing was significant for HCV

10 weeks of topical cyclosporine

25 days of glecaprevir/pibrentasvir

OSDI:	25 = moderate
Osmolarity:	301 OD 303 OS
Schirmer:	14mm OD 5mm OS

Her staining was dramatically improved



80 yowf

OSDI 88

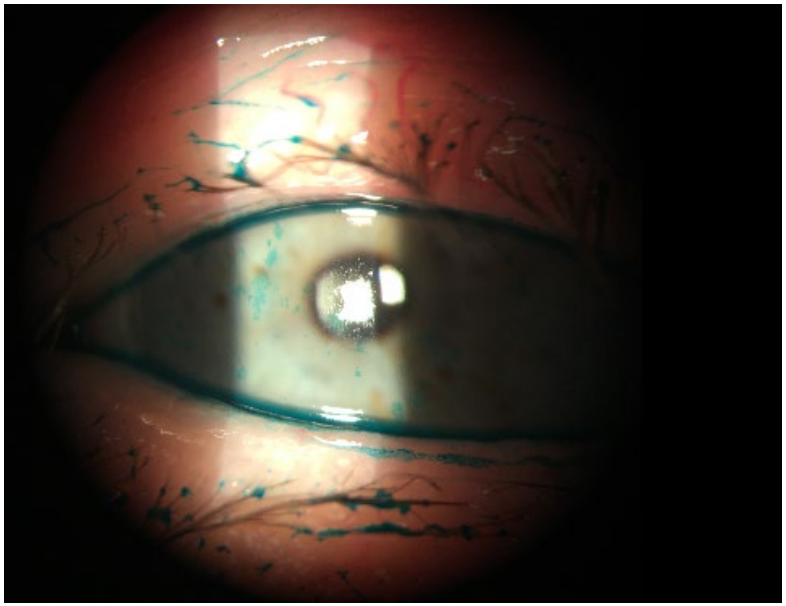
Schirmer 2,5

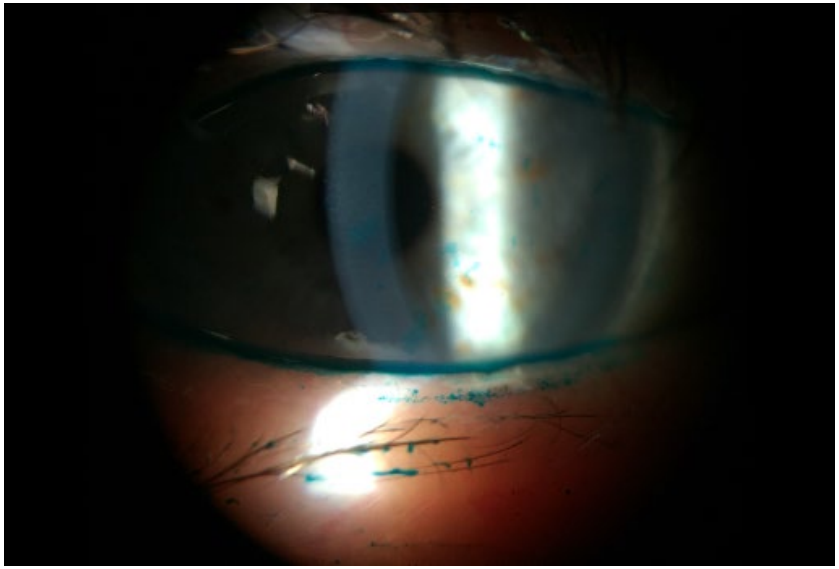
"I don't want to live if I can't see."

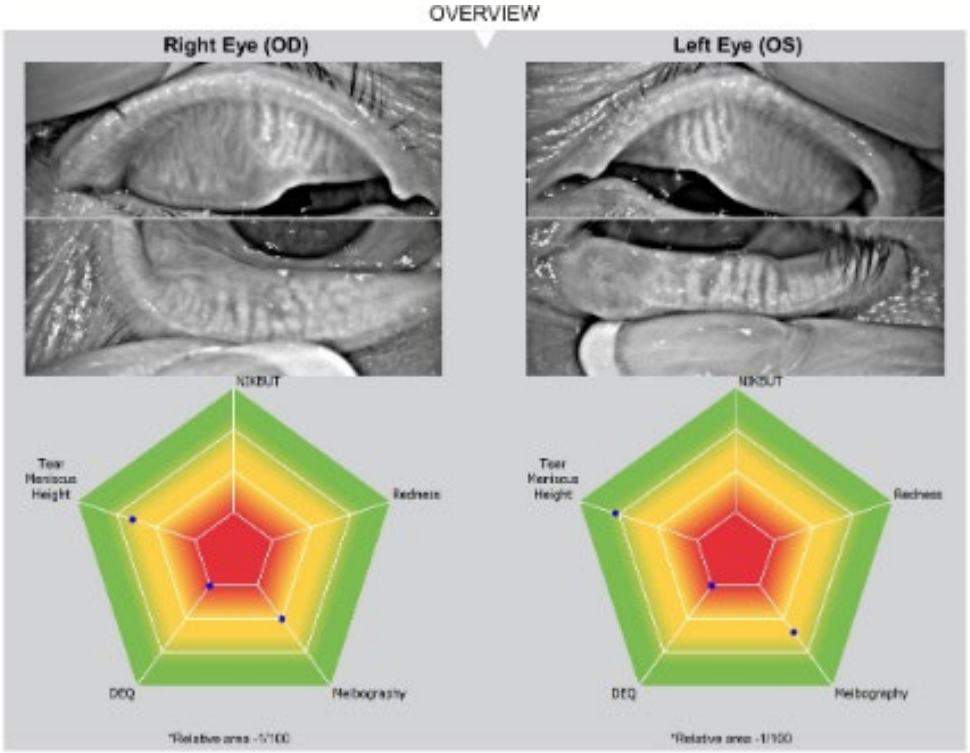
Vision fluctuating

Diagnosed with SS 15 years prior

No rheumatology care







UNIVERSITY OF PIKEVILLE

KENTUCKY COLLEGE OF OPTOMETRY

Treatments

Topical cyclosporine

Bandage contact lenses with antibiotic drops

+6.00 readers with BI to allow her to read

Tears q2hours

Tea tree teatments

Lid debridements

Oozing itching extended over al large portion of the calf and shin

Referral to rheum

Initiated oral prednisone

Suspect for leukocytoclastic vasculitis

Unable to get approval for PET scan

Over the next 3 months condition continues to worsen and colitis signs develop

Patient diagnosed with lymphoma

Summary

Systemic autoimmune disease can drive ocular inflammation

One significant manifestation is dry eye

Coordinated care is needed to enhance QOL

There are multiple advanced treatments available to reduce patient symptoms