Dry Eye and Associated Systemic Conditions

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Dry Eye Disease

- A multifactoral disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability, with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface (the International Dry Eye Workshop Study Group (DEWS)

Epidemiology

- Global presence: 3.5% to 33.7%
  - Variability due to differences in:
    - Ages studied
    - Diagnostic criteria used
  - Higher prevalence
    - Women
    - Increasing age

Etiology and Risk Factors

- Aqueous deficiency
- Lipid (evaporative) deficiency
- Mucin deficiency
- Toxicity
- Mechanical factors
- Neurotrophic component
- Other risk factors

Aqueous Deficiency

- Infiltration of the lacrimal gland
  - Sjögren’s syndrome
    - Primary
    - Secondary: associated with other auto-immune disorder
      - Rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, polymyositis
  - Lymphoma
  - Sarcoidosis
  - Hemochromatosis
  - Amyloidosis
  - Graft versus host disease

Aqueous Deficiency

- Infectious
  - HIV, human T-lymphotropic virus 1
  - Hepatitis C
  - Epstein-Barr virus
  - Lyme disease
- Systemic medications
  - Diuretics
  - Anticholinergics
  - Antihistamines
  - Antidepressants
- Previous surgery
  - LASIK/PRK
  - Cataract extraction
  - Penetrating keratoplasty
LIPID (EVAPORATIVE) DEFICIENCY
- Meibomian gland dysfunction
  - Primary
  - Rosacea
  - Posterior blepharitis, meibomitis
  - Systemic retinoids (isoretinoin)
- Low omega-3 dietary intake
- Aqueous and evaporative tear deficiency coexist in up to 60% of dry eye patients

MUCIN LAYER/GOBLET CELL DEFICIENCY
- Conjunctival scarring
  - Mucous membrane pemphigoid
  - Stevens Johnson syndrome
  - Toxic epidermal necrolysis
  - Atopic conjunctivitis (severe)
  - Graft versus host disease
- Vitamin A deficiency
  - Dietary deficiency
  - Decreased absorption: bariatric surgery

TOXICITY & MECHANICAL FACTORS
- Use of preserved eye drops >qid
- Environmental factors
  - Low humidity, drafts
  - Exogenous irritants: dust, allergens, chemicals
- Eyelid malposition, scarring, lagophthalmos
- Proptosis: thyroid eye disease, orbital process
- Local trauma: orbital surgery, radiation

NEUROTROPHIC COMPONENT
- Local effects
  - Topical anesthetics, β blockers
  - Surgery: LASIK, PRK, PKP, CE
  - Contact lens wear
  - Diabetes mellitus
- Trigeminal nerve dysfunction
  - Trauma, including surgery: trigeminal rhizotomy
  - Neoplasm: acoustic neuroma
  - Infectious: herpes zoster, simplex
- Central nervous system: cerebrovascular accident, aneurysm, demyelinating disease, dysautonomias

OTHER RISK FACTORS
- Age
- Female gender
- Asian race
- Ovarian dysfunction
- Androgen deficiency
- Postmenopausal hormone therapy
- Benign prostatic hypertrophy
- Systemic chemotherapy

QUALITY OF LIFE
- Vast array of symptoms
- Survey of 640 patients
  - 389 unique symptoms descriptions
  - Different words for "same" symptom
- Most severe symptom is often not the most frequent
- Severity increases as day progresses
Ocular Surface Disease Index (OSDI)

Have you experienced any of the following during the last week:

<table>
<thead>
<tr>
<th></th>
<th>All of the time</th>
<th>Most of the time</th>
<th>Half of the time</th>
<th>Some of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Eyes that are sensitive to light?</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2. Eyes that hurt?</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>3. Have you had trouble with your vision?</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>4. Have you had trouble seeing?</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total score for answers 1-4 (C)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Subtotal score for answers 1-5 (A)

Have you experienced any of the following during the last week:

<table>
<thead>
<tr>
<th></th>
<th>All of the time</th>
<th>Most of the time</th>
<th>Half of the time</th>
<th>Some of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>10. Windy conditions?</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>11. Places of low humidity (very dry)?</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>12. Areas that are air conditioned?</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total score for answers 10-12 (C)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Subtotal score for answers 6-9 (B)

Have your eyes felt uncomfortable in any of the following situations during the last week:

<table>
<thead>
<tr>
<th></th>
<th>All of the time</th>
<th>Most of the time</th>
<th>Half of the time</th>
<th>Some of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. Reading?</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>7. Driving at night?</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>8. Working with a computer or bank machine (ATM)?</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>9. Watching TV?</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total score for answers 6-9 (B)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OSDI Scoring

Add subtotals of A, B, and C to obtain D (D is sum of scores for all questions answered)

(OSDI = D(sum of scores) x 25)

Total number of questions answered
(Do not include questions answered N/A)

OSDI = D(sum of scores) x 25
-------------------------------------
E(# of questions answered)

Scale of 0 to 100
Higher score = worse symptoms

Tear osmolarity

- Osmometry is the measurement of the number or concentration of dissolved solutes in solution, irrespective of their size, density, molecular weight or electric charge.
- Dry eye (early stages): continuous action of compensatory mechanisms in response to environmental stress in such a way that only transient peaks of tear instability and hyperosmolarity occur.
- Dry eye (advanced stages): compensatory mechanisms fail and ocular surface parameters including tear osmolarity values remain irreversibly in the pathological ranges.

Tear osmolarity

- A voltage is applied to the tear fluid and the electrical impedance of the dissolved tear fluid particles is monitored.
- Range of the system is 270–400 mOsms/l
- 50nl of sample necessary
- Intereye osmolarity variability was demonstrated to be a hallmark of DE correlated to disease severity
- Review of literature suggests 306-316 as cut-off value for dry eye

Increased tear osmolarity has been shown to initiate and promote ocular surface inflammation and epithelial damage.
**Tear Stability/Integrity**

- Fluorescein TBUT
- Tearscope
- Kinetic topography
  - Tear stability analysis system

**Tear Stability Analysis System (TSAS)**

Software measures width of reflected ring in serial images as a measure of tear smoothness


**Tear Parameters**

- Tear volume
  - Tear meniscus measurement
    - Optical coherence tomography (OCT)
    - Phenol red cotton thread
- Tear dynamics
  - Production
    - Schirmer test
  - Clearance
    - Fluorescein clearance test

**Ocular Surface Disease**

- Ocular surface disease
  - Dye staining
    - Cornea – fluorescein
    - Conjunctiva – lissamine green
  - Cytology
    - Goblet cell density
    - Squamous metaplasia
  - Immune/inflammatory markers, HLA-DR
Impression Cytology

- Goblet cell density
- Parameters of squamous metaplasia
  - Carbon:Nitrogen ratio
  - Cohesiveness
  - Eosinophilic staining

Dry Eye Clinical Evaluation

- Complete ocular history
- Review of systems
- Medical history
- Review medications
- Osmolarity
- Schirmer testing
- Tear break-up time
- Corneal staining with Nafl
- Conjunctival staining with lissamine green

Systemic Etiology/Treatment Plan

- Consider systemic diagnoses
- Lab w/u for severe dry eye with positive Review of Systems
- Comangement with Rheumatology (auto-immune), burn service (SJS/TENS), Oncology (GVHD) to treat underlying cause
- Aggressive anti-inflammatory treatment

Thyroid Eye Disease (TED)

- Combination of adnexal and orbital findings that occurs most commonly in autoimmune thyroid disease (Graves’ disease 25-50%)
- Associated with Hashimoto’s thyroiditis, thyroid carcinoma, primary hyperthyroidism, and primary hypothyroidism
- Self-limited condition
- More common in women (5:1)

Pathogenesis/Risk Factors

- Endocrine manifestations of Graves’ disease are secondary to autoantibody formation to the thryotropin receptor causing either hyperstimulation or blockade of the receptor signaling
- Role of these thyroid-stimulating autoantibodies is unclear in TED
- Underlying pathogenesis of TED remains poorly understood
- Risk Factors
  - Environmental influences, especially smoking
  - Prior pathogen exposures
  - Stress
  - Previous use of radioiodine
  - Genetic component
### Thyroid Eye Disease

- Manifests in 2 phases:
  - Active
    - Fluctuating inflammatory course over months-years
    - Systemic corticosteroids may provide symptomatic improvement but may seldom halt the disease progression
  - Nonprogressive
    - Mainstay of treatment remains surgical
      - Orbital decompression
      - Strabismus surgery
      - Eyelid surgery

### Clinical Manifestations

- Proptosis
- Upper eyelid retraction with temporal flare
- Conjunctival injection
- Chemosis
- Periorbital edema
- Potential sight-threatening morbidities of TED:
  - Optic nerve compression
  - Primary exposure keratopathy
  - Diplopia

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### Ocular Surface Changes in TED

- Purpose: To study the incidence and risk factors of ocular surface damage in TED and to determine histological changes underlying positive vital staining in this condition
- 46 patients with TED
- Routine ophthalmologic exam, Schirmer test, vital staining, and corneal sensitivity. 15 patients with positive vital dye staining underwent impression cytology and incisional biopsy

- Positive vital staining with lissamine green was observed in 56 eyes (60.9%) of 30 patients (65.2%)
- Conjunctival changes: significant epithelial dystrophy with cell polymorphism, goblet cell loss, excessive desquamation and epithelial keratinization with local leukocytic infiltration of the substantia propria.
- Significant risk factors of ocular surface damage in TED:
  - Exophthalmos
  - Lagophthalmos
  - Palpebral fissure height
  - Lower lid retraction

### Multidisciplinary Approach

- Endocrine monitoring to maintain euthyroidism
- Definitive treatment of their underlying thyroid condition by means of radioactive therapy or thyroidectomy
- Immunosuppressive agents or biological agents
- Smoking cessation
- Ophthalmic care

### Active TED Management

- Selenium (mild cases)
  - 100µg bid
  - Trace mineral and an essential nutrient for selenocysteine synthesis, which has antioxidant properties
  - Linked to increased risk of Type II Diabetes in doses exceeding 400mcg/d
- Corneal exposure management
  - Artificial tears/ointments
  - Topical cyclosporine
  - Punctal occlusion
  - Tarsorrhaphy
Active TED management

- Systemic anti-inflammatory medications
  - Moderate-severe active TED
    - Reduction in visual acuity
    - Visual field defects
    - Color deficits
    - Afferent pupillary defect
  - Oral or intravenously
    - Macchia et al reported no significant side-effects associated with twice weekly infusions of intravenous methylprednisolone versus oral prednisone treated patients (typical steroid side-effects). Both groups achieved the same level in signs and symptoms of orbital inflammation.
- Mainstay of therapy: Corticosteroids or observation

Active TED management

- Radiation therapy
  - Controversial – reports of effectiveness of orbital radiation are quite variable
  - Viable option for patients unable to tolerate systemic corticosteroid therapy
- Rituximab
  - Monoclonal chimeric antibody against CD20
  - Effectively depletes the CD20 B-cell population for 6-9 months
  - Targeted disruption of cytokines instrumental in the pathogenesis of TED
  - Optimal dosing is unclear (100mg x 1 - 1000mg x 3-4 infusions)

Sjögren’s syndrome (SS)

- Multisystem autoimmune disease with a prevalence of 0.1-0.3% of the general population
- Characterized by lymphocytic infiltration of exocrine glands (lacrimal & salivary) and other glands
- Approximately 1/3 of patients with pSS have extraglandular systemic findings, including visceral and non-visceral manifestations.
- Increased pain, fatigue and disability, depressed mood and cognitive symptoms as compared to individuals without SS.

American-European Consensus Group 2002 revised criteria

- Requires 4 of the 6 criteria OR 3 of the 4 objective criteria
  - Subjective ocular dryness
  - Subjective oral dryness
  - Objective ocular dryness
  - Objective oral dryness
  - Presence of Sjögren-specific antibody A (SSA)/Ro and/or Sjögren-specific antibody B (SSB)/La
  - Positive minor salivary gland biopsy

American College of Rheumatology-Sjögren’s International Collaborative Clinical Alliance 2012 criteria

- Requires 2 of the 3 criteria
  - Positive serum anti-Ro/SSA and/or Anti-La/SSB antibodies, or positive rheumatoid factor and antinuclear antibody (titer>1:320)
  - Presence of keratoconjunctivitis sicca defined by an ocular staining score >3
  - Presence of focal lymphocytic salivaryitis defined by a focus score more than 1 focus/4 mm² in labial salivary gland biopsy
Autoimmunity in IL-14α

- IL-14 is a cytokine originally identified as a B cell growth factor.
- The il14 gene is located on chromosome 4.
- Production of IL-14-transgenic mice to study the role of IL-14 in the development of autoimmunity.
  - At age 3–9 mo, IL-14-transgenic mice demonstrate increased numbers of B1 cells in the peritoneum, increased serum IgM, IgG, and IgG 2a and show enhanced responses to T-dependent and T-independent Ags compared with controls.
  - At age 9–17 mo, IL-14-transgenic mice develop autoantibodies, sialadenitis, as in Sjögren’s syndrome, and immune complex-mediated nephritis, as in World Health Organization class II SLE nephritis.
  - At age 14–18 mo, 95% of IL-14-transgenic mice developed CD5 B cell lymphomas, consistent with the lymphomas seen in elderly patients with Sjögren’s syndrome and SLE.
- These data support a role for IL-14 in the development of both autoimmunity and lymphomagenesis.
- These studies may provide a genetic link between these often related disorders.

Evaluation of Patients With Dry Eye for Presence of Underlying Sjögren Syndrome

Evan Kanavarel Apek, MD, * Siona Klimas, BS, * Jennifer E. Thorne, MD, PhD,† Don Martin, MD,‡ Karolina Lukanidin, MD,§ and Ann Ostrom, MD

- Retrospective chart review of 220 patients with a primary diagnosis of dry eye syndrome (International Classification of Diseases [ICD] code 375.15 or 370.33).
- Patients who had 2 or more visits to a single dry eye center during a 2-year period were considered.
- Dry eye testing: Schirmer test without anesthesia, tear break-up time, sodium fluorescein staining of the cornea, lissamine green staining of the conjunctiva.
- Laboratory evaluation: anti-SSA/Ro, anti-SSB/La, ANA, RF, anti-5M, anti-Scl-70, and anticentromere antibodies, was performed in all suspected patients based on a positive review of systems.

### TABLE 2. Diagnosis of SS Relative to Diagnosis of Dry Eye Syndrome

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sjögren’s Syndrome</td>
<td>95.1%</td>
<td>81.0%</td>
<td>86.2%</td>
<td>98.1%</td>
</tr>
<tr>
<td>Positivity of ANA</td>
<td>94.8%</td>
<td>80.6%</td>
<td>85.7%</td>
<td>97.9%</td>
</tr>
<tr>
<td>Anti-Ro (anti-SSA)</td>
<td>94.8%</td>
<td>80.6%</td>
<td>85.7%</td>
<td>97.9%</td>
</tr>
<tr>
<td>Anti-La (anti-SSB)</td>
<td>94.8%</td>
<td>80.6%</td>
<td>85.7%</td>
<td>97.9%</td>
</tr>
<tr>
<td>Positive ANA</td>
<td>94.8%</td>
<td>80.6%</td>
<td>85.7%</td>
<td>97.9%</td>
</tr>
<tr>
<td>Positive Anti-Ro (anti-SSA)</td>
<td>94.8%</td>
<td>80.6%</td>
<td>85.7%</td>
<td>97.9%</td>
</tr>
<tr>
<td>Positive Anti-La (anti-SSB)</td>
<td>94.8%</td>
<td>80.6%</td>
<td>85.7%</td>
<td>97.9%</td>
</tr>
<tr>
<td>Positive Positivity of ANA</td>
<td>94.8%</td>
<td>80.6%</td>
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</tr>
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<td>Positive Anti-La (anti-SSB)</td>
<td>94.8%</td>
<td>80.6%</td>
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<td>97.9%</td>
</tr>
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<td>85.7%</td>
<td>97.9%</td>
</tr>
</tbody>
</table>

**Table**: Among the 12 patients diagnosed with SS as a result of the initial diagnosis:

- 66.6% (8/12) tested SSA (anti-Ro antibodies) or SSB (anti-La antibodies) positive.
- One-third of patients (4/12) tested only antinuclear antibody positive at a titer of 1:320 and required minor salivary gland biopsy for definitive diagnosis.
- 16.7% (2/12), who were initially serologically negative, eventually underwent minor salivary gland biopsy and became diagnosed with SS.

### TABLE 3. Risk Factors for the Diagnosis of SS

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.02</td>
<td>1.00</td>
</tr>
<tr>
<td>Sex (male vs female)</td>
<td>0.99</td>
<td>0.98</td>
</tr>
<tr>
<td>Race (Caucasian vs non-Caucasian)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Schirmer test &lt;5 mm</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Presence of ANA</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Presence of Anti-Ro (anti-SSA)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Presence of Anti-La (anti-SSB)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

**Significant correlation between the ANA, SSA, and SSB. However, the severity of disease parameters, age, or sex did not correlate with a diagnosis of SS.**

**Conclusions:**

- PSS seems to be underdiagnosed in patients with dry eye syndrome and should be the focus of diagnostic evaluations.
- A minor salivary gland biopsy might be required for a definitive diagnosis in a significant proportion of the patients with SS.
Prevalence and predictors of Sjögren’s syndrome in a prospective cohort of patients with aqueous-deficient dry eye

Melissa Hui-Hui Lee,1 Min Zhang,1 Elizabeth Kim,2 Gaeun K. Alpok1

Multicentre randomized, prospective clinical trial to assess the prevalence and determine predictors of Sjögren’s syndrome in patients with clinically significant aqueous-deficient dry eye

Patients: Adult patients with a diagnosis of dry eye for >/= 6 months and the following criteria were enrolled: Schirmer test without anesthesia ≥ 1 and ≤ 7 mm; sum of corneal fluorescein staining ≥ 4; moderate-severe score on the modified Ocular Comfort Index questionnaire

Clinical Trial testing

- Ocular testing:
  - Schirmer test
  - Corneal fluorescein staining
  - Conjunctival lissamine green staining
  - Tear-film break-up time
- Review of systems questionnaire
- Medical history
- Dry eye questionnaire
- Lab work-up
  - Sjogren’s-specific antibody A (SSA)
  - Sjogren’s-specific antibody B (SSB)
  - Rheumatoid factor (RF)
  - Antinuclear antibody (ANA)

Clinical Trial cont’d

Results: Of the 327 patients –
- 38 (11.6%) had SS
  - 21 (6.4%) with pSS
  - 17 (5.2%) with sSS
  - 9 newly diagnosed (American-European Consensus criteria 2002)
- Patients with SS
  - Worse conjunctival and corneal staining
  - Worse Schirmer test (with and without anesthesia)
  - Worse symptoms
- pSS was more likely to occur in patients with:
  - Positive ANA (OR:13.9)
  - Positive RF (OR:4.8)

Conclusions:
- When caring for patients with clinically significant dry eye
  - High index of suspicion for underlying SS
  - Low threshold for serological work-up
- RF and ANA are recommended as useful tests in SSa/SSB-negative patients for further diagnostic referral

Clinical Relevance of Early Diagnosis of SS

Patients expressing SSA/Ro antibodies is important because these patients are most likely to develop extraglandular manifestations, including cryoglobulinemia, vasculitis, anemia, leukopenia, and thrombocytopenia. These patients should be monitored more closely.

Patients with more severe sicca symptoms and those who develop extraglandular (systemic) disease may need to be treated more aggressively with systemic medications rather than the local measures used in those with milder sicca symptoms alone.

SS and Lymphoma

- Lymphoma is one of the most serious complications of SS (~5% of patients)
- The risk increases with durations of the disease
- Approximately 1 in 5 deaths in patients with pSS is caused by lymphoma
- Early detection is important to reduce morbidity and health care costs, and improve quality of life
Systemic therapy

- Hydroxychloroquine
  - Oral immunomodulator
  - Dosed at 6-7mg/kg per day
  - Mechanism not fully understood – attributed to interference with macrophage processing of antigens interfering with T-cell activation and possibly preventing epitope spreading for autoantibodies
  - Believed to improve salivary gland function and may prevent neoplastic transformation by modulating lymphoproliferation
  - Good safety profile, <1 in 1000 patients with macular toxicity

- Rituximab
  - Chimeric monoclonal antibody directed against the CD20 molecule
  - Administered as intravenous infusions (375mg/m²) once weekly for 4 weeks
  - Causes B-cell death by a mechanism not fully understood

- Anti-tumor necrosis factor agents
  - Single pilot study (systemic infliximab) demonstrated significant improvement in dry eye symptoms and Schirmer scores in 16 patients.
  - Subsequent prospective trials, however, failed to show objective improvement in the sicca component of SS

- Mycophenolic acid
  - Selective inhibitor of inosine monophosphate dehydrogenase, and thus inhibits the de novo pathway of nucleotide synthesis. Its antiproliferative effect occurs through inhibition of T and B lymphocytes
  - Single-center, prospective pilot trial with 11 patients with SS. Significant reduction in symptoms of dry eye but no improvement in Schirmer scores over 6 months.
  - Compared with hydroxychloroquine (control) in an open-label study of 20 patients. Lacrimal and salivary functions improved by 67% and 61% respectively, for the interferon alpha group, and 15% and 18% for the hydroxychloroquine group.

- Cyclosporine
  - Immunomodulator used in a double blind study of 20 patients with systemic findings from SS. No improvement in salivary flow or Schirmer scores after one year.

- Interferon Alpha-2
  - Compared with hydroxychloroquine (control) in an open-label study of 20 patients. Lacrimal and salivary functions improved by 67% and 61% respectively, for the interferon alpha group, and 15% and 18% for the hydroxychloroquine group.

- Corticosteroids
  - Randomized, double-masked trial with 3 arms (tx with 30mg prednisone on alternate days, 20mg piroxicam daily, placebo). No improvement in Schirmer scores nor conjunctival staining after 6 months of treatment.

- Bromhexine
  - Mixed results of multiple prospective studies have been preformed to evaluate effects on Schirmer scores, corneal and conjunctival staining, along with tear composition.

Secretagogues

- Pilocarpine
  - Salagen tablets(5 and 7.5mg tablets); most patients require 20mg/d in divided doses for therapeutic response
  - Muscarinic cholinergic parasympathomimetic agonist that binds to M3 receptors and stimulates exocrine glands
  - Cevimeline hydrochloride
  - Evoxac (30mg tablets) dosed 3 times daily
  - Derivative of acetylcholine that binds M3 receptors in exocrine glands

Dry Eye Treatment

- Lubricants
  - Artificial tears/ointment
  - Preserv-free when utilizing >QID
  - Muro 128 (corneal dystrophy/recurrent corneal erosion)

- Corticosteroids
  - Lotemax, Flurometholone
  - provide high ocular surface drug concentrations and are able to promote lymphocyte apoptosis and suppress cell mediated inflammation
  - Monitor closely for IOP increase, cataract, corneal thinning, and infectious keratitis
**Dry Eye Treatment**

- Cyclosporine A
  - Restasis 0.05%, Compounded 1%
  - Dosed two (or more) times daily
  - Reduces inflammation, via inhibition of T-cell activation and down-regulation of inflammatory cytokines in the conjunctiva and lacrimal gland → allow enhanced tear production
  - Increases goblet cell density and decreases epithelial cell apoptosis
- Serum tears
  - Serum contains several anti-inflammatory factors that have the capability to inhibit soluble mediators of the ocular surface inflammatory cascade of dry eye.

- Tacrolimus
  - Available in 0.03% and 0.1% ointment and compounded drops and systemically
  - Inhibits T and B lymphocyte activation by reducing interleukin-2 synthesis
  - Also suppresses immune response by inhibiting the release of other cytokines as well
- Oral immunosuppression
  - Immune-mediated ocular surface disease (Sjogren’s syndrome, graft versus host, Stevens Johnson syndrome)

**Dry Eye Treatment**

- Punctal occlusion
  - Collagen or Silicone / Cauterization
  - Use of anti-inflammatory prior to occlusion
- Bandage contact lens
  - Silicone hydrogel
  - Filamentary keratitis/Exposure
- Surgical management of eyelids
  - Tarsorrhaphy
  - Repair of eyelid positioning
- PROSE treatment

**Intense Pulse Light (IPL)**

**Lipiflow**
**What is PROSE?**

- Prosthetic replacement of the ocular surface ecosystem (PROSE)
  - To restore vision, support healing, reduce symptoms, and improve quality of life
  - FDA-approved custom designed and fabricated prosthetic devices to replace or support impaired ocular surface

**PROSE Benefits**

- Re-establish healthy and stable ocular surface
  - Support healing and reduce symptoms
- Improve blurry vision
  - Mask surface corneal irregularities
- Prevent damage by protecting and shielding the cornea and conjunctiva against the environment and eyelids

**PROSE Design**

- Creates a smooth optical surface over the irregular, damaged or diseased cornea
- Expanded artificial tear reservoir provides constant lubrication while maintaining necessary oxygen supply

**PROSE Use**

- Daily Wear
  - Exception healing PED
  - I&R education important component of fitting process
  - Horizontal, fluid filled insertion with plunger
  - Device removed with removal plunger

**Prose Care**

- Nightly disinfection
  - Optimum Extra Strength Cleaner
  - Clear Care in custom BFS case
- Rinsing and insertion
  - Rinse with sterile saline
  - Insertion with Unisol 4 sterile saline
  - Replaced every 48 hrs
- Clean plungers daily with alcohol swab

**IRREGULAR ASTIGMATISM INDICATIONS FOR PROSE TREATMENT**

- Ectasia
- Keratoconus
- Post-surgical irregular astigmatism
- Keratoglobus
- Post-LASIK scarring
- Horners marginal degeneration

- Post-Op
  - Topical medications
  - Phototherapeutic keratectomy, LASIK, photorefractive keratectomy

- Scarring
  - Top tretenon
- Top cortisone
- Top hydrops

- Cornual dystrophy
  - Basal corneal dystrophy
  - Nesteren corneal dystrophy
Ocular Surface Disease Indications for PROSE Treatment

<table>
<thead>
<tr>
<th>Dry eye syndrome</th>
<th>Chronic graft-versus host disease</th>
</tr>
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<tbody>
<tr>
<td>Sjogren syndrome</td>
<td></td>
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<tr>
<td>Rheumatoid arthritis</td>
<td></td>
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<tr>
<td>s/p orbital radiation</td>
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<tr>
<td>s/p LASIK</td>
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</table>

Neurotrophic cornea

<table>
<thead>
<tr>
<th>Familial dysautonomia</th>
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<tbody>
<tr>
<td>Acoustic neuroma</td>
<td></td>
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<tr>
<td>Trigeminal ganglioneuroma</td>
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<tr>
<td>Herpes simplex</td>
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<tr>
<td>Herpes zoster</td>
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</table>

Ocular Surface Disease Indications for PROSE Treatment cont.

<table>
<thead>
<tr>
<th>Corneal stem cell</th>
<th>Steven-Johnson syndrome/</th>
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</thead>
<tbody>
<tr>
<td>Deficiency</td>
<td>toxic epithelial necrolysis</td>
</tr>
<tr>
<td>Dermal ocular disorders</td>
<td>Ocular cicatricial pemphigoid</td>
</tr>
<tr>
<td>Epidermolysis bullosa</td>
<td>Aniridia</td>
</tr>
</tbody>
</table>

Ectodermal dysplasias

<table>
<thead>
<tr>
<th>Lagopthalmos</th>
<th>Anatomic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paralytic</td>
<td>Persistent epithelial defect</td>
</tr>
</tbody>
</table>

Traditional Scleral Lenses

PROSE Design: Spline Functions

- Corneal clearance can be adjusted independently of the BC

Case - Patient with Severe Dry Eye Secondary to Exposure

Before | 4.5 hrs after removal
Treatment of PED's

- Retrospective chart review 13 patients (14 eyes)
  - EW
  - 12/14 Ab and steroid added to lens

- 5/7 SJS healed
  - Repeat PK, EW
  - Healed after 3 days but recurred

- 3/7 non-SJS patients healed
  - Healed after repeat amniotic membrane grafts

A Novel Drug Delivery System

- Corneal neovascularization can lead to deterioration of vision and increased surface irregularities
- Bevacizumab, anti-VEGF drug
  - FDA approved 2004 for metastatic colorectal cancer
- Report of 5 patients DW PROSE device and twice daily 1% Bevacizumab in the lens reservoir
  - Corneal clarity and vision improved in all patients
  - No adverse effects reported

What the Patients can expect

- PROSE Referral form completed with last 2-3 exams
  - Phone: 410-955-5257
  - Fax: 410-955-0867
  - www.hopkinsmedicine.org/wilmer/news/PROSE.html
- Initial PROSE consultation visit
  - Examination
  - Device trial and determination of candidacy
- If patient is a candidate:
  - Insurance pre-determination
    - Letter of medical necessity
  - Start fitting
  - Global period

References